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American Heart Journal

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Original Communications

THE HEART IN RHEUMATOID ARTHRITIS

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NEW YORK, N. Y.

THERE is a fairly extensive literature concerning cardiac changes in rheumatoid arthritis. Much of the interest in this subject has stemmed, on one hand, from a belief in the fundamental relationship of rheumatoid arthritis to rheumatic fever; and, on the other, from the clinical observation of acute pericarditis in appreciable numbers of individuals with rheumatoid arthritis. In general, it may be said that most clinical studies have failed to bring out the presence of a high incidence of rheumatic heart disease (Table I), while most pathologic investigations have indicated that the two diseases coexist frequently (Table II). The apparent discrepancy has not been satisfactorily explained to most observers.

The present paper attempts to elucidate the factors that are concerned in the disparity between these various reports. It is based upon a study of pathologic material from 101 cases of rheumatoid arthritis. Sixty-six of these are from the files of the Armed Forces Institute of Pathology. Another thirty-five are from Bellevue Hospital, New York. Dr. Milton Helpern kindly granted permission to study three of these. Inasmuch as only nineteen of these have been observed first hand, the interpretations have been made from protocols written by others, and from review of such histologic sections as were available in each instance. This is one of several treacherous features common to the present and other papers concerning this problem. In the great majority of cases, the diagnosis of rheumatoid arthritis was well documented clinically. In a number of instances, the clinical information was meager. Such cases were accepted as rheumatoid only if the clinical diagnosis was made unequivocally and not con-

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TABLE I. CLINICAL STUDIES, HEART IN RHEUMATOID ARTHRITIS

AUTHORS		NO. CASES	NONSPECIFIC ABNORMALITY (%)	RHEUMATIC HEART DISEASE (%)	CONTROL
Boas & Rifkin	(1a)	80	13.8	17.5 (including M.I.*) 10 (excluding M.I.)	
Master & Jaffe	(1b)	17	17.6	0	
Master & Jaffe	(1c)	50	—	0	
Bayles	(1d)	—		5	
Kahlmeter	(1e)	37 ("secondary")		24	4.4% of 68 acute infectious diseases
		48 ("primary")		8.3	
Kuhns & Joplin	(1f)	452		2.2	0 of 198, osteoarthritis
Dawson & Tyson	(1g)	—		7	
Colver	(1h)	69 (juvenile)		1.4	
Monroe	(1i)	267		4	
Ellman	(1j)	100		8	
Feiring	(1k)	27		29	
Pickard	(1l)	35 (juvenile)		5.7	
Lucchesi, and others	(1m)	50		0	
Rogen	(1n)	33		3	
Edstrom	(1o)	65 (juvenile)	45	1.5	
Fischmann & Gwynne	(1p)	60	44		
Losada & France	(1q)	136		2.9	
Robles Gil	(1r)	36		10.2	
Bernstein & Broch	(1s)	352 (Marie-Strumpell)		2.8	
Jonsson, and others	(1t)	40	30	2.5	
Rosenberg, and others	(1u)	147	3.4	0	0%
Bradfield & Hejtmancik	(1v)	45	15.7	2.2	
Schneller	(1w)	100	36	0	
Barkin	(1x)	51 (juvenile)	21	9.4	

*M. I. = mitral insufficiency.

tradicted by other clinical or pathologic data. The inclusion of these cases has not affected appreciably the incidence of rheumatic heart disease in the entire series. Two instances of chronic, deforming polyarthritis were excluded because they ultimately gave evidence of being associated with disseminated lupus erythematosus. Ankylosing spondylitis has been accepted as rheumatoid arthritis of the spine. There were seventeen such instances in the present series; in eleven of these, peripheral joints were involved also.

To help crystallize present thinking about this problem and to simplify discussion, three aspects have been considered: (1) the occurrence of rheumatic heart disease in rheumatoid arthritis, (2) the existence of specific rheumatoid heart disease, and (3) the occurrence of pericarditis.

TABLE II. PATHOLOGICAL STUDIES, HEART IN RHEUMATOID ARTHRITIS

AUTHORS		NO. CASES	MINIMAL RHD	TOTAL RHD (%)	CONTROL (NONRHEUMATOID) (%)
Kast 1901	(2a)	19		21	
Grzimek	(2b)	91		42.8	17.9
Baggenstoss & Rosenberg	(2c)	25		56	
Baggenstoss & Rosenberg	(2d)	30		53	
Bayles	(1d)	23		26.1	
Fingerman & Andrus	(2e)	61		31	
Young & Schwedel	(2f)	38		65.7	
Graef and others	(2g)	66	(36.3)	39.4	
Bywaters	(2h)	(27)*		(18.5)*	8
		23		7	

*Including postrheumatic type (Jacoud).

RHEUMATIC HEART DISEASE

A major source of difficulty has been the lack of a definitive diagnostic test for rheumatic inflammation. As a result pathologists have employed varying criteria for the diagnosis of rheumatic heart disease. Although few persons would doubt that mitral stenosis, for example, is the consequence of rheumatic valvulitis, the significance of minor sclerotic and inflammatory changes in the heart is highly debatable. Competent pathologists may find so-called "stigmata" of rheumatic inflammation in perhaps 60 per cent to 93 per cent of the general adult population at necropsy[3]. Gross sclerotic changes in the chordae tendineae of the mitral valve that are not ordinarily regarded as rheumatic[4] may also be found in a large number of older persons' hearts. Although it is not possible to disprove the contention that these "stigmata" are evidences of old or latent rheumatic carditis, their frequency in individuals without rheumatoid arthritis is so great as to preclude their usefulness in clarifying the present problem. For this reason, three categories of rheumatic heart disease have been distinguished in the present study: (1) frank rheumatic heart disease, such as mitral stenosis, rheumatic valvulitis and myocarditis with formation of Aschoff bodies; (2) minimal rheumatic heart disease, in which minor sclerosis of the valves was accompanied by histologic demonstration of fibrosis of the leaflet with formation of thick-walled blood vessels; and (3) calcareous stenosis of the aortic valve. The last group is considered to have a rheumatic etiology by most American pathologists at the present time[5]; it is not, however, classified as such by the New York Association.[6]

For purposes of comparison with the occurrence of rheumatic heart disease in an unselected general population, data have been obtained from consecutive necropsies performed on 1,154 persons over 19 years of age dying at Bellevue Hospital in 1950 and 1951. All but four of the necropsies on the rheumatoid group were performed between 1942 and 1952; sixty-seven between 1947 and 1952. Sections of at least one heart valve were available in 39 per cent of the cases from the Armed Forces Institute of Pathology and 51 per cent of those from Bellevue Hospital. It is well known that there are marked differences between the sexes in the incidence and character of the valvular involvement in

rheumatic heart disease.[7] There were sixty men in the group from the Armed Forces Institute of Pathology, and seventeen in the Bellevue group. Recognition of the variation according to sex has been taken by presenting the total incidence of rheumatic heart disease, in Tables III and IV, both in absolute figures and in figures adjusted for the proportion of men and women. The latter value is obtained by computing the average of the incidence in each sex independently.

TABLE III. INCIDENCE OF RHEUMATIC HEART DISEASE, 1,154 CONSECUTIVE NECROPSIES ON PERSONS NINETEEN YEARS OF AGE AND OLDER BELLEVUE HOSPITAL

	812 MEN		342 WOMEN		1,154 TOTAL		WEIGHTED % FOR SEX*
	NO.	(%)	NO.	(%)	NO.	(%)	
Frank rheumatic	22	2.71	17	4.97	39	3.38	3.84
Minimal rheumatic	6	0.74	5	1.46	11	0.95	1.11
Calcareous aortic stenosis	14	1.72	2	0.58	16	1.52	1.15
Total rheumatic	42	5.17	24	7.02	66	5.72	6.10

*Average of incidence in men and women.

It it seen in Tables III and IV that the incidence of rheumatic heart disease is somewhat higher in the group with rheumatoid arthritis than in the general autopsy series. It is obviously far less than that reported in most of the papers summarzied in Table II. Actually a number of factors undoubtedly introduce elements of selection in the figures. For this reason there is little point to make an extended statistical analysis of them. Similar influences are undoubtedly present in the aforementioned studies and require evaluation.

TABLE IV. INCIDENCE OF RHEUMATIC HEART DISEASE, 101 CASES OF RHEUMATOID ARTHRITIS IN PERSONS NINETEEN YEARS OF AGE AND OLDER

	77 MEN		24 WOMEN		101 TOTAL		WEIGHTED % FOR SEX*
	NO.	(%)	NO.	(%)	NO.	(%)	
Frank rheumatic	1	1.3	4	16.6	5	5.0	9.0
Minimal rheumatic	1	1.3	0	0.0	1	1.0	0.7
Calcareous aortic stenosis	4	5.2	0	0.0	4	4.0	2.6
Total rheumatic	6	7.8	4	16.6	10	9.9	12.2

*Average of incidence in men and women.

1. Although the number of cases of rheumatoid arthritis in the present study is larger than in any other report, it is, nevertheless, relatively small.

2. The fact that the data from the Armed Forces Institute of Pathology have been drawn principally from military personnel suggests that a proportion of persons who contracted rheumatic heart disease prior to the age of induction has been excluded. On the other hand, it appears likely that such personnel has,

at times, a predisposition to develop rheumatic fever as the result of epidemics of infection with hemolytic streptococci.[8,9]

3. Only coded cases have been available for review. The diagnosis of rheumatoid arthritis at times does not find its way to the front sheet of the protocol of necropsy. In many instances, the arthritis is a relatively inconspicuous part of the picture that causes the patient's admission to the hospital. This tends to make the coded case studied here be a severe one. One may suspect that the coexistence of rheumatoid arthritis with rheumatic heart disease on a medical service creates a circumstance that does not allow the diagnosis of the former to be overlooked. The reason for this is that internists are, in general, quite alert to the present problem. An analagous consideration has been presented by Bayles[1d]: many rheumatoid cripples die at home instead of in the hospital unless heart disease supervenes. A similar opinion has been expressed by Jonsson and associates.[1t]

4. The diagnosis of rheumatoid arthritis in a large proportion of cases has not been established anatomically. Extensive dissection of the joints is not commonly performed at necropsy in this country. Even when sections are available, the changes may be quite nonspecific. Bywaters[2h] has suggested that a large proportion of individuals, ordinarily believed to have rheumatoid arthritis coexisting with rheumatic heart disease, do not have rheumatoid arthritis at all. Theirs is, rather, a deforming, postrheumatic arthritis. The existence of such an entity is not commonly accepted in this country. Pathologic data that might bear on it are not available in the present series.

5. In addition to the various sources of error discussed above, there is a risk of bias in sampling demonstrated in clinical studies by Berkson[9] and illustrated with reference to autopsy surveys in the accompanying article by Mainland.[10]

If recognition is made of all these limitations, the results of the present investigation suggest that in individuals with rheumatoid arthritis, there may be a somewhat higher incidence of heart disease, indistinguishable from rheumatic heart disease, than chance would dictate. The number of cases of rheumatoid arthritis studied is not great enough to prove conclusively that this is so. It should be kept in mind that rheumatic heart disease in a general population includes a large group of individuals in whom the heart disease is not the principal cause of death. At Bellevue Hospital, somewhat less than one-half the cases of rheumatic heart disease can be regarded as incidental to some other lethal disease. This may increase the significance of the relatively frequent association of the two conditions. We are encouraged to believe that it accurately reflects an appreciable predisposition for rheumatic heart disease to be found in association with rheumatoid arthritis because of the agreement of these data with those of other acceptable published and unpublished studies.

The nature of this association cannot, of course, be inferred from these observations. Some factor, either in the nature of the disease or in the constitution of the individual subject to it, may be involved. There appears to be some similar slight predisposition for disseminated lupus erythematosus, polyarteritis nodosa, and chronic peptic ulcers to coexist with rheumatoid arthritis.

There remains the question: why have not most clinical studies confirmed this observation? To this it may be replied that the disparity is not as great as the uncritical interpretation of the pathologic diagnosis of rheumatic heart disease would suggest. A large proportion of the reported instances of rheumatic heart disease, if not dubious, are of minimal severity. There are important limitations to the accuracy of clinical diagnosis of rheumatic heart disease even when the valvular deformity is severe. This is particularly true in the older patients. In one group of twenty patients over 60 years of age who had rheumatic heart disease, a correct clinical diagnosis was made only eight times.[11] Kumpe and Bean[12] observed that it was made in only 28 per cent of their cases of proved aortic stenosis. In the present series, the correct clinical diagnosis was made only four times, although there were nine anatomically proved cases of rheumatic heart disease. This incidence of 4.0 per cent is not far from that reported in Table I.

RHEUMATOID HEART DISEASE

During the course of the past few years, a concept of heart disease, quite specific to rheumatoid arthritis, has evolved. This is characterized by granulomatous inflammation similar to that found in the rheumatoid subcutaneous nodules. Such foci have been observed in the epicardium,[13a,b] adjacent myocardium,[13b] and in the rings and leaflets of the mitral and aortic valves.[2b,d,g; 13a,b; 16] Bevans[14] has observed early mitral valvulitis in an individual with widely disseminated rheumatoid granulomata. This was characterized by necrosis and acute inflammatory reaction and did not resemble rheumatic valvulitis. We have seen a similar lesion in a case of rheumatoid arthritis at another institution. In the present series, there is at least one convincing case of rheumatoid nodule formation in the material from the Armed Forces Institute of Pathology. It appears that the incidence of such frank rheumatoid heart disease is, perhaps, about 1 per cent to 3 per cent of the cases of rheumatoid arthritis. Graef and associates[2g] have described two instances of involvement of the coronary arteries in a lesion resembling polyarteritis nodosa. There is some evidence that disseminated arteritis is a manifestation of rheumatoid arthritis.[15a,b] The relationship this bears to the coronary arteritis described by Graef is not clear at this time. He also observed minute granulomata in the myocardium that were regarded to be analagous to the Aschoff body of rheumatic myocarditis. Focal involvement of the myocardium has been observed by Baggenstoss and associates.[17]

While it is conceivable that healed or minor lesions may lead to deformities indistinguishable from those of rheumatic heart disease, the proof for this is lacking at present. Nodular deformity of the valve may lead to its incompetence. The lesion described in the aortic valve by Pirani and Bennett[18] may well be such an instance. Bauer and associates have observed aortic insufficiency as a manifestation of ankylosing spondylitis.[19] This lesion was not present in the seventeen instances of spondylitis in the present series.

PERICARDITIS

The frequent occurrence of adhesive pericarditis has been recognized in virtually all the pathologic studies referred to,[1d, 2b, g] although it is observed clinically far less commonly. In Table V is charted the incidence of pericarditis in the 101 cases of rheumatoid arthritis compared to that in the control group of 1,154 necropsies at Bellevue. Inasmuch as it has been possible to assign an etiology to the great majority of nonrheumatoid cases, the data have been broken down as to whether the pericarditis in the cases of rheumatoid arthritis could be attributed to some cause other than the rheumatoid disease.

TABLE V. INCIDENCE OF PERICARDITIS (IN PER CENT)

TYPE OF PERICARDITIS	RHEUMATOID ARTHRITIS			1,154 CONSECUTIVE NECROPSIES AT BELLEVUE
	AFIP* (66)	BELLEVUE (35)	TOTAL (101)	
Fibrous pericardial obliteration, etiology unproved	18.2	25.7	20.8	0.7
Fibrous pericardial adhesions, etiology unproved	3.0	5.7	4.0	1.0
Total healed pericarditis, etiology unproved	21.2	31.4	24.8	1.7
Fibrinous pericarditis, etiology unproved	0	0	0	0.5
Miscellaneous pericarditis, etiology proved	19.7	8.6	15.8	6.6
Pericarditis, all types	40.9	40.0	40.6	8.8

*AFIP = Armed Forces Institute of Pathology.

It appears that patients with rheumatoid arthritis had evidence of healed, idiopathic pericarditis more than seventeen times as commonly as other types of individuals had. A certain percentage of the pericarditis is accounted for by intercurrent disease not primarily related to the arthritis. Up to some point, rheumatoid arthritis may predispose in some manner for pericarditis to complicate intercurrent disease. On the other hand, there is a large group of patients in which such a pathogenesis cannot be implicated. Frankly granulomatous pericarditis is known to occur in rare instances of rheumatoid arthritis. We may properly speculate that the frequency of fibrous pericardial obliteration in this condition speaks for a burned-out rheumatoid pericarditis. The occurrence of fibrous serous adhesions without residual specific lesions is well recognized in other granulomatous inflammations, such as tuberculosis. As in the case of healed serosal tuberculosis, what proportion of the rheumatoid pericarditis was at one time granulomatous and what proportion fibrinous cannot be estimated.

SUMMARY AND CONCLUSIONS

This report is a critical investigation of the apparent discrepancy between the reputedly high incidence of rheumatic heart disease in pathologic studies of rheumatoid arthritis and its infrequency in clinical studies. It is based upon

pathologic data from 101 cases of rheumatoid arthritis. Several sources of error in determining the incidence of rheumatic heart disease are pointed out. It appears that there may be a slightly greater than fortuitous coincidence of heart disease in rheumatoid arthritis morphologically indistinguishable from rheumatic heart disease. In addition, the concept of a specific rheumatoid heart disease emerges. The frequency with which evidences of healed pericarditis are found indicates that pericarditis is a common, cardiac manifestation of rheumatoid arthritis.

Dr. Alvin S. Mund and Dr. Barbara S. Sokoloff gave valuable assistance during certain phases of this study.

Addendum: Since this manuscript was written, four additional patients with peripheral rheumatoid arthritis have been studied. Calcareous aortic stenosis was present in one of three men; the woman had healed, rheumatic inflammation of the mitral valve. The incidence of rheumatic heart disease in 105 patients with rheumatoid heart disease is: frank rheumatic, 5.7 per cent; minimal rheumatic, 1.0 per cent; calcareous aortic stenosis, 4.8 per cent; total rheumatic, 11.5 per cent.

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THE RISK OF FALLACIOUS CONCLUSIONS FROM AUTOPSY DATA ON THE INCIDENCE OF DISEASES WITH APPLICATIONS TO HEART DISEASE

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IN 1946 Berkson,[1] Medical Statistician at the Mayo Clinic, published a paper of profound importance to all who study the etiology and interrelationships of diseases in human beings. Berkson's demonstration had reference to clinic and hospital patients in the search for an association between diabetes and cholecystitis. There was such a strong impression of the existence of this association that some surgeons were removing the gallbladder in the treatment of diabetes. To test the soundness of the belief, the incidence of cholecystitis in diabetic patients was compared with its incidence in persons who came to the clinic for eye testing, because it could not reasonably be suspected that there was any association between cholecystitis and errors of refraction.

The frequency of cholecystitis was found to be higher in the diabetics by an amount that was statistically significant, i.e., greater than investigators are prepared to attribute to chance. Berkson showed, however, that such results could be entirely fallacious under two conditions which must very often exist. In brief these are: (1) that the occurrence of two disorders in the same person gives him an increased probability of admission to a hospital or clinic, and (2) that the persons with the disorders under investigation are not represented in the hospital or clinic population in the same proportions as in the general population.

The same kind of bias can affect any other comparisons from hospital records, such as the incidence of heart disease in two occupational classes; and the bias can also prevent the detection of a real association.

The importance of the demonstration is well recognized by those who are acquainted with it; but six years after its publication, if one can judge from research papers brought to statisticians for analysis, or sent to statistical referees by editors of medical journals, the demonstration has not yet become widely known, perhaps because it appeared in a statistical journal. It does not, however, depend on complex or theoretical considerations, either statistical or medical, and indeed it is not confined to medicine but applies to any kind of investigation that involves sampling. As its author himself pointed out, "the same results . . . would occur if the sampling were applied to . . . cards instead of patients." More recently[2] he expressed the situation in general terms: Although we have long recognized hospital samples as biased samples (not representative

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of the general population of sick people) we have been slow to recognize the simple corollary, that unbiased conclusions about the relationships of two diseases cannot be derived from such biased samples.

Berkson's demonstration is starting to appear in the courses and textbooks on medical statistics,[3] but this is a slow and devious method of propagation. It seems necessary to bring the fallacy directly to the attention of investigators, and that is the purpose of this article. The application will be to autopsy studies because of the author's recent contact with several of them, laborious and time-consuming, but leading to very questionable conclusions because this fallacy was ignored. Clinical readers who are unfamiliar with Berkson's work will, however, be able to see from the discussion how the bias can occur in their own fields.

A SIMPLIFIED EXAMPLE

In order to avoid stigmatizing any particular piece of work, or obscuring the general principle by side issues pertinent to particular diseases, we shall use the letters *A*, *B*, and *X* to represent diseases; and in order to show the essentials we shall first use a simplified example.

Let us suppose that there are two diseases, *A* and *B*, and that we wish from autopsy records to find whether another disease, *X*, is more common in persons with *A* or in persons with *B*. Let us further suppose that the percentage frequency of *X* in the general population is exactly the same, 10 per cent, in *A* patients and in *B* patients. Indeed, we could even assume that this same percentage applied throughout the population, whether persons had *A* or *B* or neither of those diseases.

We can remove some potential bias by supposing that all deaths are subject to autopsy, that we have all the autopsy reports, and that the only causes of death in the population are *A*, *B*, and *X*. For further simplicity we suppose that there are equal numbers of *A*'s and *B*'s, 1000 of each, in the general population. There are, therefore, 100 *A*'s who have *X* and 900 *A*'s who do not have *X*; and the same numbers apply to the *B*'s, i.e., 100 *B*,*X* and 900 *B*,*not-X*.

We take the case fatality rate for *A*, i.e., the percentage of *A*'s who die from that disease in the period under survey, as 50 per cent; for *B*, 20 per cent; and for *X*, 40 per cent. We now calculate how many will die in each group.

Group A,*X*.—Total patients = 100. Fifty per cent of them, i.e., 50 patients, die of *A*, leaving fifty alive. Of these fifty, 40 per cent, i.e., 20 patients, die of *X*. Total deaths = 70.

We note that, of the fifty who die of *A*, twenty would otherwise have died of *X*; or, alternatively, we can think of *A* and *X* as killing simultaneously, as "multiple" causes of death. In any case the total number of deaths is not affected; nor is it affected if we count first the forty who die of *X* and then take 50 per cent of the remaining sixty persons to give thirty deaths from *A*.

Group A,*not-X*.—Total patients = 900, of whom 450 die of *A*.

Group B,*X*.—Total patients = 100. Twenty per cent, i.e., 20, die of *B*, leaving 80 alive. Of these 80, 40 per cent, i.e., 32, die of *X*. Total deaths = 52.

Group B,not-X.—Total patients = 900, of whom 180 die of *B*.

In summary, the cadavers to be investigated can be displayed in a fourfold table thus:

	X	*not-X*	Total
A	70	450	520
B	52	180	232
Total	122	630	752

The percentage frequencies of *X* are as follows:
Of the *A*'s, $70 \times 100/520 = 13.46$ per cent have disease *X*.
Of the *B*'s, $52 \times 100/232 = 22.41$ per cent have disease *X*.
Difference = 8.95, or approximately 9 per cent.

In an actual investigation we should ordinarily test the above fourfold table in order to show how far chance could account for the difference. Chi-square = 8.81, and the probability of meeting such a value when chance alone is operating is less than 0.01 (less than 1 chance in 100—in fact, it is less than 1 chance in 300).

Note.—(1) For increased accuracy, in the calculation of chi-square the adjustment called "Yates's correction" was used. (2) If the equivalent standard error test (also with Yates's correction) is employed, it gives the ratio (difference : standard error of difference) = 2.97; and the probability of chance occurrence is, of course, exactly the same as with chi-square.

Whatever standards of statistical significance we might customarily adopt, with such a low probability we should feel convinced that chance alone was not responsible. And yet we know, in this present case, that in the parent population the percentage frequency of *X* in the *A*'s and the *B*'s was exactly the same. The fault is not in the statistical test. Such tests never claim to do more than show how often certain things would occur if chance (i.e., random variation) alone were responsible. Here the chi-square test has shown, quite correctly, that if two samples, of the sizes given, were taken strictly at random from the same population, the observed differences would occur very rarely. We should rightly conclude, therefore, that something more than chance was operating; but we should be wrong if we thought that this "something" was a closer association in the parent population between *X* and *B* than between *X* and *A*. The "something" is in reality a bias in the sampling, due to the lower fatality of *B*, which causes a higher proportion of the dead *B*'s to be afflicted with *X* than is found among the dead *A*'s. The phenomenon can be described as a competition among fatality rates. The rate in *A* offers stronger opposition to *X* than does the rate in *B*; i.e., more of the *B*'s are left to be killed by *X*.

Obviously, if the fatality rates in *A* and *B* were reversed the opposite picture would be obtained—a greater frequency of *X* in the *A*'s. Also, if *X* were actually more frequent in the *A*'s in the parent population, but the fatality due to *B* was, as in our example, less than the fatality due to *A*, the true relationship might be masked, or even apparently reversed, in the autopsy study.

EFFECT OF CHANGES IN NUMERICAL VALUES

In its simplified form the fallacy is obvious. Under actual conditions the risk is not reduced, but the picture is very complex. Before trying to penetrate

this complexity the reader is recommended to become thoroughly familiar with the simple phenomenon by substituting different numerical values in the above example, such as different fatality rates and sample sizes. If he is familiar with the chi-square (or standard error) test of significance he will find it instructive to apply it to each of his examples. The results of such changes can be illustrated as follows.

If the samples were larger than in the original example, but the proportions remained the same, the difference (approximately 9 per cent) would, of course, remain; but chi-square would be larger, and the probability of chance occurrence would be less. If the samples were only half the original size but the proportions were again the same, chi-square would be only 4.1, which is just above 3.84, the value usually required for significance (1 chance in 20).

Further reduction in sample size would lead to the verdict: no significant difference between the frequency of X in the A's and in the B's. This is not, of course, an indication that the autopsy survey method can be trusted for small samples. On the contrary, it emphasizes the existence of bias, for it leads to the paradox whereby with smaller samples, i.e., less information, we seem to come nearer the truth (no real difference between A's and B's in the frequency of X) than with larger samples, i.e., more information, obtained in the same way. Similarly, reduction of the difference between the fatality rates in A and B reduces the bias, but a significant difference still emerges when the samples are large enough.

The introduction of deaths from other causes than A, B, and X takes the simplified data a step nearer actual conditions. The reader could add to the assumptions of the original example the further assumption that, of those who did not die of A, B, or X, 10 per cent died of other causes, while still affected by one or more of the three original diseases. Step-by-step calculation, like that shown above, would then reveal that at the autopsies 12.85 per cent of the A's and 18.39 per cent of the B's would have X.

APPLICATION TO ACTUAL CONDITIONS

The essential features of the simplified example are: (1) that two diseases, A and B, have different fatality rates, (2) that disease X is neither more nor less closely associated with A than with B, and (3) that X has a lethal effect. It need not be able itself to kill a patient but merely to lessen his resistance to other diseases. These features must be common under actual conditions, but there it will be seen that the same principle of competing rates has a much more extensive application. This can be illustrated under four headings: (1) associated mortality; (2) other selection factors—(a) ante-mortem, (b) post-mortem; (3) pooling of diseases; and (4) competition of incidence rates and fatality rates.

1. Associated Mortality.—The diseases labeled A, B, and X need not actually cause death or even lower the resistance to other diseases. Indeed, the conditions so labeled need not be diseases at all, but some harmless anatomic or physiologic feature, or some environmental feature, such as occupation. For the bias to occur, all that is necessary is that the conditions be present with different frequencies in groups with different general death rates. If, for instance, in the

original example *A* indicated older people, and *B* much younger people, and if the case fatality rate of *X* were the same in both, or only slightly greater in the *A*'s, the higher general mortality in the older persons would cause the appearance of a higher incidence of *X* in the younger subjects at autopsy. (Later, it will be appreciated that even *X* need not be a disease if it is some feature that causes differential selection of deceased subjects for autopsy.)

This bias due to differences in associated mortality indicates one way of trying to reduce the risk of bias—by subdividing the data into classes according to age, sex, race, and other features, such as occupation or socio-economic level, that are known or suspected to have differences in death rates.

Recognition of the risk of bias from associated mortality makes obvious also the danger of comparing, with respect to *X*, the *A*'s and the *B*'s when these two were not observed in the same region, hospital, or period of time.

The division into narrow groups, for comparison of the incidence of *X* in *A* and *B* within each group, produces a large number of small samples. In some of the samples *A*, *B*, or *X* may be missing, but it is better to discard those samples than to reintroduce the risk of bias by pooling them again with other samples.

The statistical testing of such material is not necessarily very difficult, but the serious difficulty is to know when all relevant subdivisions have been made. For example, racial classification would generally be coarse, but even such features as differences in arterial patterns are found to occur with different frequencies in different subdivisions of broad racial groups.

2. Other Selection Factors.—Under actual conditions it is not only death that determines whether or not a subject is brought to autopsy. To the fatality rates and general death rates already discussed must be added other selection rates which will compete with them and with each other. Two classes of such factors can be distinguished: (a) ante-mortem, and (b) post-mortem.

(*a*) *Ante-mortem Factors.*—As is well known, the composition of a hospital population is determined by numerous factors, ranging from the reputation of an individual specialist to the fees charged for hospital care. The effect of such selection is, of course, carried through to the autopsy division and may affect differentially the three diseases, *A*, *B*, and *X*. Search could be made for a few of these sources of bias, but many of them must remain undiscovered.

(*b*) *Post-mortem Factors.*—The simplified example showed bias occurring, although all deceased subjects were sent to autopsy. Under actual conditions, even after death in a hospital or elsewhere, selection factors intervene, such as physicians' interests in particular cases or certain types of disease, difficulty in ante-mortem diagnosis causing the demand for an autopsy, the attitudes of relatives and undertakers, and the legal requirements pertaining to certain types of death.

Clearly, efforts to remove such bias from data already obtained can have little success. The only solution would be to avoid the bias by compulsory autopsy of all deceased patients or of a sample of such patients selected by an automatic random sampling process such as a table of random numbers.

3. Pooling of Diseases.—It is a common custom to compare the incidence of *X* in disease *A* with its incidence, not in one other disease, but in all other

autopsies. Anyone who starts to think about the causes of bias discussed above will realize how such bias can enter at numerous points in a mass comparison. The hope that pooling all diseases will cause the various biases to cancel each other is a vain hope.

In studying the incidence of X in A it may be desirable to consider not only B but other diseases, C, D, and so on, in order to obtain more material and more than one standard of comparison; but in any such attempt the incidence of X in all the chosen diseases, including A, should first be examined. The appropriate tabular form would have column headings for X (present or absent) and row headings for A, B, C, and so on.

4. Competition of Incidence Rates and Fatality Rates.—The original example was kept simple by implying that the events (occurrence of disease, death, or recovery) took place within a short period of time. Alternatively, one can assume acute diseases that either killed the patients or left no lesion that could be discovered at autopsy in subsequent years. Many of the conditions studied at autopsy, however, are permanent lesions that may have occurred years previously. Then, the frequencies of X at autopsies in the A's and B's, even in any one age group, are affected not only by differences in the respective fatality rates at that time, but by (a) the differences in the proportions of cases that have escaped death at earlier ages, and (b) the differences in incidence of new cases in each previous age period.

To gain some idea of the resulting complexity one can try to imagine (a) that the residual living subjects of the original example came to autopsy at a later time, still bearing the lesions of A, B, or X; (b) that at that time the fatality rates differed from the earlier rates; and (c) that to them at autopsy were added subjects (of the same age) who had incurred the diseases more recently or earlier than the original series, i.e., when incidence rates were different.

These various factors could so act as to produce in all age groups at autopsy a higher frequency of X in the B's than in the A's, although X had been at all times allocated in equal proportions among the A's and B's during life. On the other hand, a real association between X and B could be entirely hidden by factors of the same type but differing in direction or degree. It is obviously impossible from autopsy information alone to measure or eliminate bias of this kind.

ILLUSTRATIONS DERIVED FROM A STUDY OF CARDIAC LESIONS IN RHEUMATOID ARTHRITIS

Because of the very nature of the phenomena, involving numerous selection factors that are known to exist but cannot be isolated or measured, no examples of the bias fully worked out are available. When the bias becomes widely recognized individual instances will be found easily. In the meantime it can be shown how such factors might have acted during the production of data such as are discussed in Sokoloff's[1] article.

Dr. Sokoloff has shown various unsatisfactory features in the background of the data available to him but has refrained from discussion of the possible effects of competing selection rates in order that his material might be used for purposes of illustration here. Speculation on the numerous possibilities would be fruitless, but it may be instructive to note how some of the factors already mentioned might have introduced bias even under more satisfactory conditions, such as the collection of all data at one hospital and in the same period. It is not implied that the factors discussed are those most likely to have caused bias in this particular study, because, as is commonly true, the information available to the investigator did not permit even a rough guess at the probable factors, much less an assessment of their relative importance.

Rheumatic Heart Disease.—Considering first the higher frequency of rheumatic heart disease in the subjects with rheumatoid arthritis than in the series of consecutive autopsies, we may imagine what would happen If physicians were not at all interested in obtaining autopsies on

arthritics unless there were present some other disease, such as heart disease, in which current interest was great. The other autopsy series would contain many conditions not found in the arthritics, and therefore the incidence of the selected diseases (including heart disease) among the arthritics would be fallaciously high.

On the other hand, a real association between rheumatic heart disease and arthritis might be partly masked at autopsy. Let us assume that there is in life a higher incidence of rheumatic heart disease in the arthritic patients than in the nonarthritics, but that arthritis tends to lower resistance to other diseases (not often fatal themselves) and to bring patients with those diseases to autopsy.

Because intricate interactions are often clarified by gross exaggeration, let us imagine that rheumatic heart disease is the only disease that brings subjects to autopsy unless, coexistent with another disease, there is arthritis. Then all the nonarthritic cadavers would have heart disease, whereas many of the arthritic cadavers would not. Under actual conditions the same tendency may operate, although with much less force, and the possibility raises questions that cannot be answered from autopsy data alone.

Simplifying Sokoloff's figures slightly for illustration, let us suppose that rheumatic heart disease was found in 10 out of 100 arthritic cadavers and in 66 out of 1,200 nonarthritic cadavers (5.5 per cent). The difference would not be considered statistically significant, for the probability of chance occurrence, found from chi-square, is greater than one-tenth. Meeting such a record we cannot tell whether it indicates that in the parent population there was actually no difference in the incidence of rheumatic heart disease in arthritics and nonarthritics, or whether a real difference has been reduced by the effect of arthritis when coexistent with other diseases, causing a disproportionate increase in the noncardiac cases in the arthritic cadavers.

Pericarditis.—Sokoloff's second main topic, the incidence of "pericarditis of unproven etiology" in arthritics, raises a question such as may be often asked in such surveys: Does not the magnitude of the difference in frequencies, 24.8 per cent in arthritics as compared with 1.7 per cent in the consecutive autopsies, prove that there is a real association, not merely an effect of biased selection? This may well be so, but we have no means of determining what size of difference is required to justify this conclusion. In considering the problem, the following two points may be noted:

1. Even if we can safely assume that the numbers of subjects with pericarditis were not increased (or decreased) by the deliberate choice (or rejection) of such subjects for autopsy, it is impossible to say how far the choice or rejection of subjects with other diseases or features in some way associated with pericarditis may have introduced bias.

2. Rheumatoid arthritis has a low direct fatality rate and can be considered as an extreme type of disease *B* in the original example. Most cases would be brought to autopsy by other diseases. Healed pericarditis has, apparently, only a slight direct deleterious effect, but we do not know what reduced resistance may persist, residual from the active phase, or caused by some associated condition, for the etiology is unknown. This factor, perhaps helped by other diseases, might play a considerable role in bringing arthritics to autopsy; i. e., it could be represented by *X* in the original example, although with a lower fatality rate.

The diseases that brought the nonarthritics to autopsy would correspond to disease *A*, and some of them (e.g., cancer) would have very high intrinsic fatality rates, which would render the pericarditis (or its associated conditions) almost negligible as a cause of death; i.e., few or none would be left to be killed by pericarditis. The effect, as in the original example, would be an artificially high frequency of pericarditis in the arthritics.

This effect provides an instructive contrast to the masking effect discussed above in connection with rheumatic heart disease, where other diseases with low fatality rates were assumed. In actual surveys there is a wide range in fatality rates among the diseases grouped as *A*, and because the difference of incidence of *X* between *A* and *B* cadavers depends considerably on these fatality rates, this adds another to the many reasons why different surveys (with different composition of the group called *A*) arrive at very diverse estimates of the differences in incidence of *X*.

To what extent these various factors may have accounted for the relatively high incidence of pericarditis in the arthritics one cannot ascertain. Perhaps the simple interpretation, a cardiac manifestation of rheumatoid arthritis, is correct, but acquaintance with the phenomena of com-

peting selection rates makes one realize that perhaps the high frequency should be corrected downward, and the amount of the correction is undeterminable. Apparent confirmation by other autopsy studies of relative incidence would still leave the question open, for the same type of bias might affect all.

POSSIBILITIES OF AVOIDING BIAS

The further one penetrates into the mass of competing selection rates the more dismayed one becomes by the confusion and by the resulting risk of fallacious inferences regarding disease incidence, leading in turn to erroneous conclusions regarding etiology and the relationships between diseases. Clinical investigators, as Berkson showed, run the same risks, and those who are investigating clinically healthy subjects do not escape the danger.*

By prolonged study of groups of living subjects in health and disease, however, there is a much better prospect of estimating and eliminating the risks than in pure autopsy studies, and cardiovascular surveys of the living have made much progress in method. An appreciation of the requirements and difficulties of such investigations can be obtained by anyone, even if unacquainted with statistical techniques, who studies a recent article on coronary heart disease in medical practitioners[5,6] and many of the papers presented at the Milbank Memorial Fund Conference in 1951.[7] In autopsy studies, when the dangers become more widely known, there may be some improvement in methods of overcoming these difficulties in the simpler cases, if indeed any cases are simple. In the meantime, suggestions can be only general and somewhat tentative.

Attempts at Numerical Correction.—If incidence rates and case fatality rates, by sex, age, racial group, and other relevant subdivisions were known for the diseases under investigation in the portion of the population that provided the autopsy subjects, an attempt could be made to introduce corrections for these two selection rates. Such direct information, however, is seldom available, and the corresponding information from official vital statistics or from private investigations cannot be assumed precisely applicable to the subjects under study. In fact, it would usually be difficult to choose, from the often widely divergent published estimates, one that would be most appropriate. For the numerous other selection factors it is, with rare exceptions, unlikely that numerical correction terms could be obtained.

Prevention of Bias by Design of Investigation.—If the diseases to be studied are such that they either kill the patient or, after recovery, leave no trace to be found at autopsy, the only way to avoid bias in the comparison of incidences appears to be the prolonged study of living subjects, already mentioned.

Diseases which, even if they do not kill, leave a permanent lesion discoverable at autopsy, can be considered as a second group. Here again the only completely satisfactory method would be to start with a group at birth (or before birth) and follow them all to autopsy. The question therefore arises: How

*Lest it be thought that this emphasis on the risks of fallacy is merely the opinion of a statistical analyst who is hypercritical of other investigators, it may be mentioned that the author is equally perturbed by analogous fallacies in his own investigations of clinically healthy subjects. He is, however, not pessimistic about future developments. The last decade has witnessed the development of sound methods of therapeutic trial by statistical planning that were previously thought inapplicable in human medicine, and if the dangers of some of the current methods in pathology become fully appreciated it can be hoped that more valid methods will replace them.

safely can this impracticable longitudinal method be replaced by a transverse (horizontal) method—autopsies on all age groups at a particular time? Anyone who is about to use this transverse method should prepare a list of the necessary assumptions, i.e., his beliefs that a particular type of bias either does not exist or will not account for his findings. This list should not be a kind of lip service, to be forgotten as soon as paid, but a constant warning to himself and to the readers of his report. It would be specifically applied to his problem, but it should include reference to the following four items:

1. Secular Changes.—All replacements of longitudinal studies by transverse studies raise the problem of secular changes, i.e., changes that have occurred with the passage of time. Because of secular changes in the environment, including hygiene and therapeutics, a man who dies at age 20 this year is not equivalent medically to a man who would have died at age 20 in a longitudinal study that was started 50 years ago, whereas a man who died at age 50 this year could actually have been in that study. Fatality rates, incidence rates, and numerous other selection factors have changed so much in the last few decades that it is clearly questionable to assume that secular changes are irrelevant in an autopsy study of incidence.

2. Competition of Incidence Rates and Fatality Rates.—The previous discussion under this heading indicates that, except perhaps in rare instances, it would be impossible to disentangle the effects of these two factors and justify the assumption that they had not introduced serious bias.

3. Other Ante-mortem Selection Factors.—Reference has already been made to the proper method of avoiding bias due to differences in sex, age, race, socioeconomic level, and other relevant features—subdivision of the data into appropriate subclasses. After this has been done, the assumption must be made that no relevant feature has been overlooked.

Included in this group of factors is the tendency for a specialist in a certain field to increase the hospital population disproportionately with patients who have a certain class of diseases, for example, *A* in contrast to *B*. To a greater or less extent, this probably affects most hospital populations; but it should be recalled that selection of *A*'s in preference to *B*'s does not cause fallacious inferences regarding the relative incidence of *X* in these two conditions unless the selective process affects *X* also, as in the example (of post-mortem selection) developed from Sokoloff's data on rheumatic heart disease in arthritics (p. 635). The assumption that physicians' interests are not a biasing factor is, therefore, safest when *X*, or any condition or feature associated with *X*, is not a criterion of admission to the hospital.

4. Post-mortem Selection.—The foregoing assumptions would all be required even if autopsies on all patients who died in a certain hospital were compulsory, or if, to save labor, a strictly random sample of all deceased patients was compulsorily autopsied. The ordinary method of selection for autopsy is not random; therefore another group of assumptions is necessary—that the selection factors entering at this stage will not cause a fallacious inference. The information available for testing this assumption is usually meager and nebulous.

Onus on the Investigator.—Despite this formidable array of assumptions it may be asserted that much of our knowledge of pathology and clinical medicine has been built on observations of relative frequencies and that the dangers described here have been exaggerated. The answer is that in each investigation the onus is on the investigator to try to prove that the dangers are negligible—to present evidence in favor of his assumptions, not merely to say that he sees no reason for doubting them. By carefully considering the assumptions and seeking for evidence in their favor he will discover that the apparent simplicity of figures extracted from autopsy or other hospital records is very deceptive. Thus he will come to realize, as is now being realized more and more widely, that although such records have immediate uses, clinical and administrative, they have very limited value for fundamental research.

If the investigator still wishes to use disease incidence in autopsy records as a possible clue to the etiology or interrelationships of diseases, he will know that, however complete and accurate the records may be, they cannot legitimately be said to give anything more than an impression—that at best the comparison of incidence may provide a hint that can be followed by methods less open to question, such as histopathology, histochemistry, animal experimentation or a well-planned long-term clinical investigation, including special techniques (such as biopsies where possible) and autopsy checks on ante-mortem diagnoses.

In the field of post-mortem pathology itself, an example is provided by the observation that the granulomatous character of pericarditis in rheumatoid arthritis is very similar to that of the subcutaneous nodule. This suggests the search for methods, such as chemical or physical techniques, that would enable one to reveal fundamental similarities and differences between structures that are superficially alike—a more satisfactory line of approach than further autopsy studies of the incidence of pericarditis in arthritics.

Without some indication other than that given by differences in autopsy incidence, however, it would seem unwise to embark on a large research project. It would be equally, or even more, unwise to consider negative results from an autopsy survey of incidence as a contraindication of further research by better methods if there is some other hint, for example from clinical observation, that the research might be fruitful.

Statistical Tests.—If this is the status of conclusions from autopsy data on disease incidence, it is questionable whether these data should receive statistical tests. Applied with clear knowledge of what their verdicts mean and do not mean, the tests are harmless, but when this knowledge is lacking they often have an undesirable effect on the mind of the investigator. When a difference is found to be statistically significant, although he may still say that bias by selection factors may be present, he is inclined to feel that the verdict has proved the likelihood of this bias to be small—that, in spite of any bias, some "real" etiological or other relationship is very probably responsible for his figures. As the first simple example showed, this is an entirely erroneous inference.

Equally erroneous is the conclusion that is often drawn when a difference is found to be nonsignificant. The investigator then is very likely to feel that he has good evidence that no "real" difference exists. He overlooks the fact that biased selection may haye prevented the appearance in autopsy material of a large difference in incidence in the living population.

If, with proper knowledge of their meaning, tests of significance are applied, this should not be done until subsampling (division by sex, age, and other relevant features) has removed at least some of the possibilities of bias. If the tests are omitted the reason should be made clear—that the data may contain much hidden bias and are, therefore, not worth testing.

SUMMARY

Berkson has shown how the bias that makes hospital populations unrepresentative of the general population of sick persons vitiates conclusions from hospital populations regarding the relationships of diseases to each other. In order to demonstrate how this fallacy can occur in autopsy data a simplified example was constructed, involving diseases *A*, *B*, and *X*, with different case fatality rates. Disease *X* in the general population was assumed present in equal proportions of *A*'s and *B*'s, but *B* killed a lower proportion of patients than *A*, leaving more *B*'s to be killed by *X*. Consequently there was at autopsy a higher percentage frequency of *X* in the *B*'s than in the *A*'s.

Under actual conditions, numerous factors besides fatality rates can produce the same effect, such as age, sex, race, socio-economic level, disease incidence rates, the factors that determine admission to a hospital and those that cause selection of deceased patients for autopsy.

Competition among these selection rates is very complex, and only a small part of the resulting bias can be measured or avoided. Therefore, if an investigator wishes to use autopsy data on disease incidence as a possible clue to the etiology or interrelationships of diseases, he should first make a list of his assumptions regarding the absence or unimportance of bias from the various sources. He should use the method merely as a first step toward more reliable methods (for example, histopathology, histochemistry, animal experimentation, or long-term clinical investigation), and he should note that the bias may mask a real association as well as create a fallacious one.

In order to avoid the overemphasis of a principle that needs none and to insure that the various aspects of the problem were correctly and sufficiently treated, an early draft of this paper was submitted to Dr. Berkson for his comments, and the author is very grateful to him for his critical reading of it. To his own colleagues, Mrs. Lee Herrera and Miss Marion I. Sutcliffe, he owes thanks for constructive suggestions during the preparation of the paper.

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ELECTROCARDIOGRAPHIC MIRROR PATTERN STUDIES. III.

Mirror Pattern Cancellation in Normal and Abnormal Subjects

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IN THE PRECEDING studies[1,2] the validity of the dipole theory was investigated by means of cancellation of mirror patterns at opposite locations in regard to a theoretical center in the heart. Ideally the potentials of opposite direction would cancel out in our experimental arrangement provided they were in phase. The degree of cancellation, as expressed in a coefficient, could then be used as a criterion for the validity of the dipole theory. It was found that, in general, the dipole theory is a useful concept and that, in our opinion, the deviations from the prediction, although definitely measureable, are not large enough to invalidate the concept.

Proof of the reasonable validity of the dipole theory in normal subjects as tested by the cancellation of mirror patterns does not, however, automatically imply applicability of the theory to patients.

The question arises as to how far local patterns as produced by local lesions may interfere with the validity of the dipole theory as a general concept of electrocardiographic interpretation. While the existence of local patterns does not necessarily conflict with the dipole theory in general, it would interfere with its predictive value from chest surface leads. In other words, it is conceivable that the dipole theory might be valid, within reasonable limits, in normal subjects but not in patients; or it might be valid in some categories of cardiac pathology and not in others. Schaefer's recent work on the theory of chest leads is also of interest in this respect. In this work, Schaefer[3] concludes that a 3:1 ratio of local potentials to remote potentials is extremely improbable. As this degree of nondipolarity would constitute an entirely uncancellable signal by our method we conclude that this degree of local response is seldom if ever found.

Another limitation of the validity of the dipole theory in patients is the definition of the electrical center of the heart. The normal volume of the heart, about 600 c.c.[4] is by no means negligible in regard to the dimensions of the thorax. A shift in the electrical center during the Q-T interval is possible in normal subjects

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(we have some experimental evidence that the center of the T wave is different from that of the ventricular complex), but these shifts may be exaggerated in patients.

The present study was undertaken in order to examine the situation in thirty-seven patients with various types of pathology.

METHOD AND MATERIAL

The technique has been described in the two preceding communications.[1,2] The results are expressed in terms of a cancellation coefficient, arbitrarily expressed in steps as excellent "E" from 0.00 to 0.08, good "G" from 0.08 to 0.12, fair "F" from 0.12 to 0.16, poor "P" from 0.16 to 0.20, and bad "B" > 0.20. The cancellations refer to the QRS complex. No effort was made to cancel the P or T wave.

The abnormal material consisted of four patients with posterior and four patients with anterior wall myocardial infarct, four patients with right bundle branch block (RBBB) and four patients with left bundle branch block (LBBB), nine patients with pulmonary emphysema, five patients with right ventricular strain and four patients with left ventricular strain, and three patients with miscellaneous cardiac pathology, totaling thirty-seven patients. Each patient with infarct, bundle branch block, or ventricular strain presented the classical pattern of these lesions. The normal material consisted of seventeen subjects.

Since the method is time consuming and tedious, it is harder to obtain a number of satisfactory cancellations in patients than in normal persons because their condition often limits the time of experimentation.

RESULTS

Figure 1,*A* shows the over-all results of 106 cancellations in seventeen normal subjects and of 142 cancellations in thirty-seven patients expressed as per cent incidence of cancellation coefficients (abscissa). In patients, the number of excellent and good cancellations was smaller and that of bad cancellations was greater. The poorer cancellation in patients is, in part, due to experimental limitations. On the average, 6.2 reference patterns were cancelled on each normal and only 3.8 on each patient.

The chance of obtaining satisfactory cancellations increases, of course, with the number of cancellations which can be tried. In view of this situation it is important that, as a whole, excellent and good cancellations could be obtained in a sizeable number of patients, and that there is no significant decrease of incidence from good to excellent cancellations. The curves in normal persons as well as in patients start with maximum incidence at excellent cancellations and decline from there to the poorer cancellations (higher coefficients).

Figure 1,*B* shows the distribution of cancellation coefficients when averaged for each individual. The curves are more symmetrical than those in Fig. 1,*A*, with a flatter maximum and greater spread in patients. The curves follow a distribution which indicates statistically that a superior cancellation in one direction does not necessarily imply superior cancellations in other directions in the same individual.

Remembering that a good cancellation has, in general, a greater weight than a poor cancellation, the over-all distribution in Fig. 1 seems to indicate that the dipole theory applies reasonably well to patients as well as to normal persons, but also that there are probably some factors which account for the greater incidence of poor and bad cancellations in patients. It would be logical to suggest that the poorer cancellations may be due to interference of local patterns.

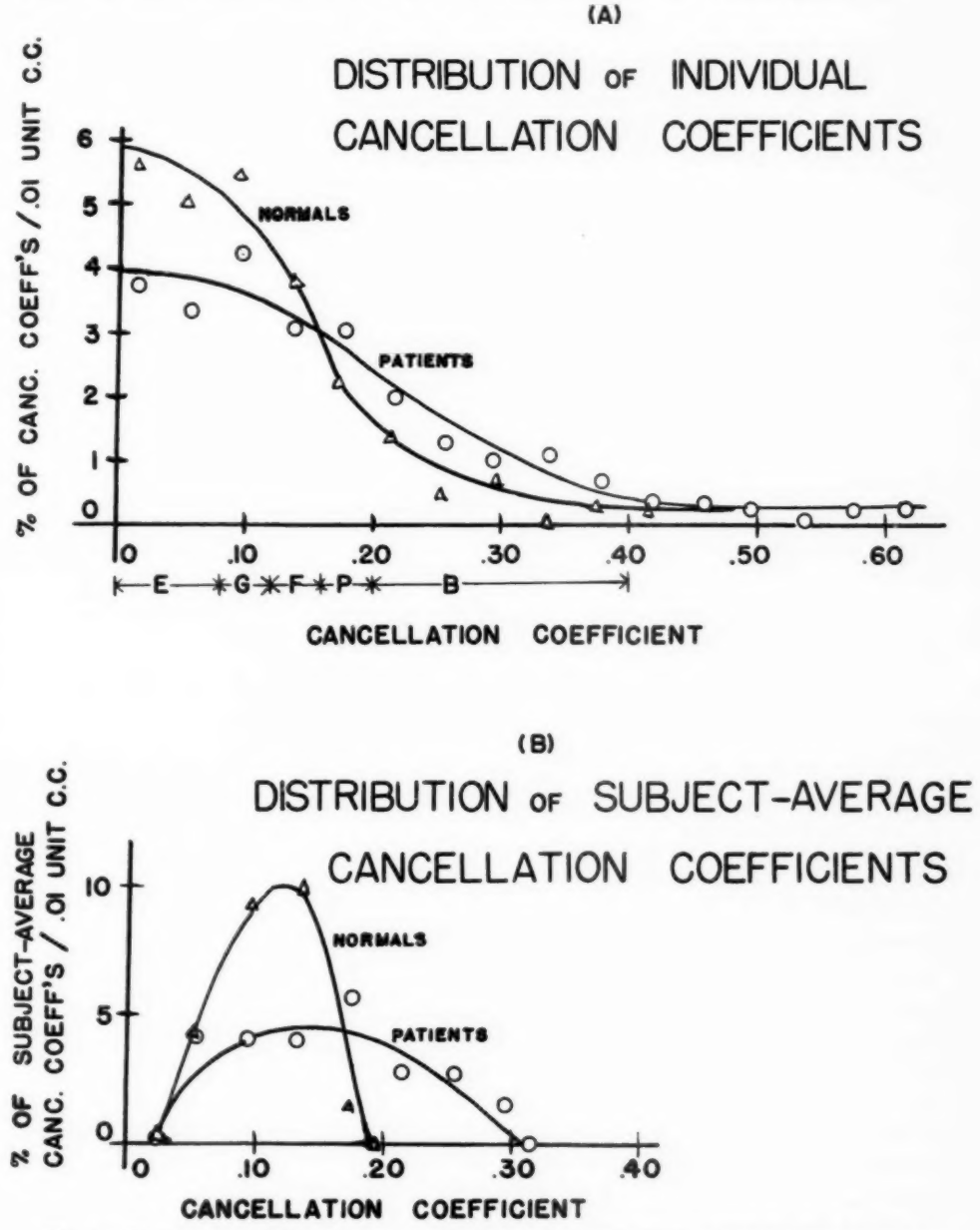

Fig. 1.—Distribution of total number of cancellations in normal persons and patients *A*, and averaged for each subject *B*. The ordinate refers to the percentage of cancellations found for each per cent (= .01 unit) of the total range of cancellation coefficients.

For a more detailed analysis, the incidence was plotted separately for the different categories of patients (Fig. 2). Of special interest are the results in the patients with a myocardial infarct, because they represent, more than any other category, localized lesions. If the poorer cancellations in patients are due to local patterns, we should expect especially poor cancellations in this group. However, the distribution of cancellations in patients with myocardial infarcts follows the normal distribution.

Table I shows the mean cancellation coefficients with standard deviations, calculated from the individual means in normal persons and in patients. The mean cancellation coefficient in normal persons and patients with a myocardial infarct is identical. This result does not support the hypothesis of local pattern interference.

TABLE I.

GROUP	NO.	M.	S.D.	M.D.	t.
Normal	17	.111	.037	—	—
Infarct	8	.117	.056	+.005	<1.0
BBB	8	.207	.045	+.095	5.51**
Emphysema	9	.143	.054	+.032	1.81
Ventr. Strain	9	.145	.041	+.034	2.16*

Means (M) and standard deviations (S.D.) of the cancellation coefficient in normal subjects and various categories of patients; mean differences (M.D.) between normals and patients and their statistical significance (+ values). **Highly significant ($p < 0.01$); *significant ($p < 0.05$).

On the other hand, the distribution curve in patients with bundle branch block has the opposite trend to that of normal persons (Fig. 2). The mean cancellation coefficient is definitely higher, and the mean difference between normal persons and this group of patients as tested by means of the t-test, is statistically highly significant (Table I).

We believe that it is the shift in the location of the dipole during the QRS complex which accounts for the poorer cancellation in patients with bundle branch block. A mobile dipole was demonstrated by Duchosal and Grosgurin[5] in some of their material, and it should be especially pronounced in patients with bundle branch block. While the theory of mirror patterns and cancellation does not depend on any definite location of the dipole, a shift would make it impossible to have a single electrode location optimum for all phases of the cycle. We often found that a shift of the search electrode from the optimum location by as little as one-half inch produced a definite deterioration of cancellation.[2] A shift of the dipole inside the heart from right to left ventricular activation or vice versa by 4 or 5 cm. would easily account for a shift in the location of optimum cancellation of one inch or more. The results in patients with bundle branch block were probably derived from this effect rather than from failure of the dipole theory.

The distribution of cancellations in patients with emphysema or ventricular strain pattern shows a minimum at intermediate cancellation coefficients (Fig. 2). In other words, the cancellation tends to be either excellent or bad. We

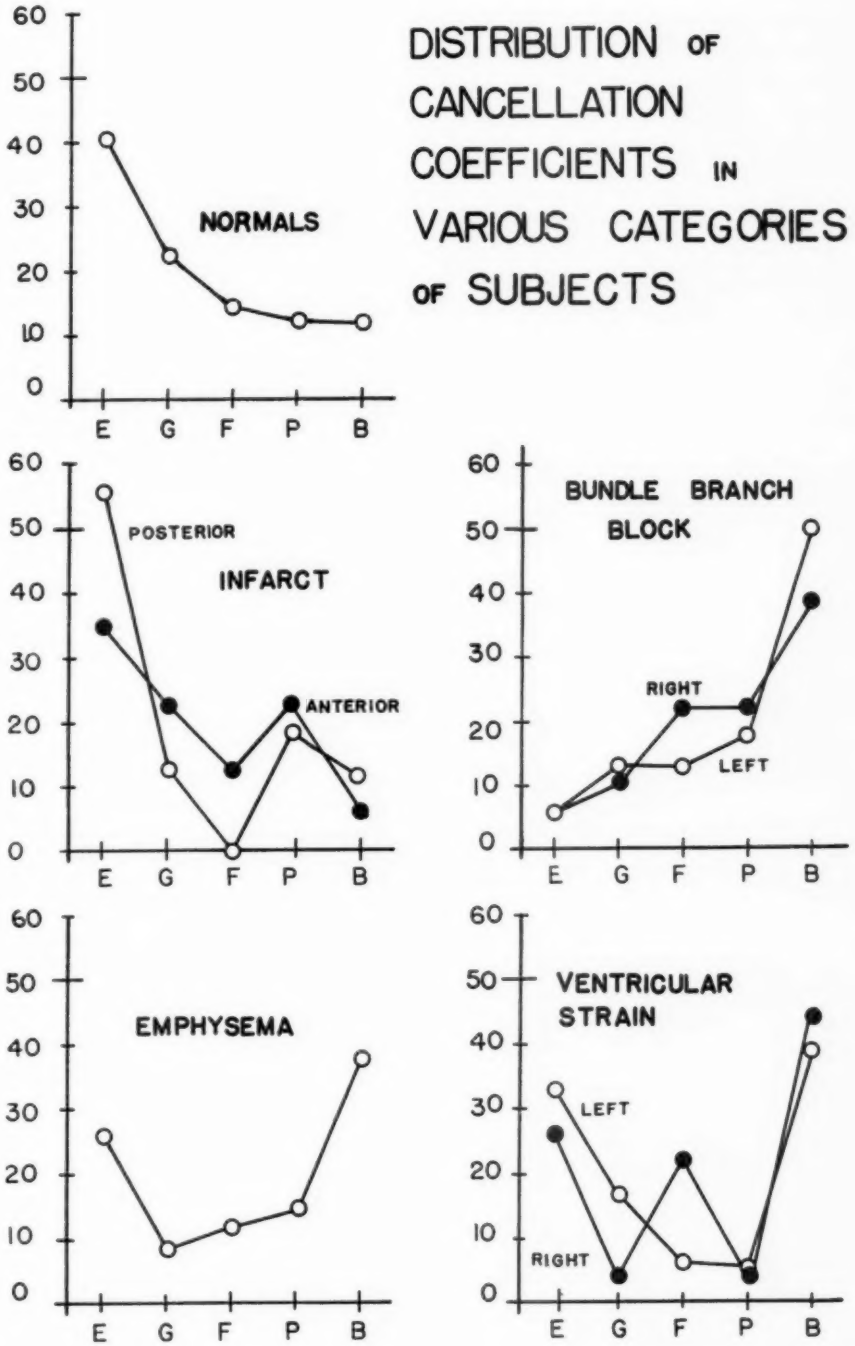

Fig. 2.—The ordinates represent percentage of cancellations for various categories of cancellation coefficients from excellent *E* to bad *B*.

believe that the high incidence of bad cancellations is, in part, due to experimental limitations. All emphysema patients were in an advanced phase of the disease, and most patients with ventricular strain were in a state of partial cardiac decompensation. The mean cancellation coefficient was somewhat higher than that in normal subjects in both groups, but statistically significant from normal only in patients with ventricular strain (Table I).

The question of possible local pattern interference was also approached from the analysis of the regional distribution of cancellations. The results are presented in scatter diagrams (Fig. 3). The Roman numerals (ordinata) refer to the horizontal level in terms of intercostal space; "zero" means above the first rib, "−I" clavicular level, "L" left leg, and "H" head. The Arabic numbers (abscissae) refer to vertical coordinates; "4" and "10" to left and right midaxillary lines, "7" midline back, "1" midsternal line. The locations are given in terms of intercepts between horizontal and vertical coordinates; thus V_4 means intercept between the fifth horizontal and fourth vertical coordinate. For cancellations on the right arm, left arm, left leg, right leg, and head, the following locations were given, in the above order: $I\frac{1}{2}_{10}$; $I\frac{1}{2}_4$; L_3; L_{11}; H_7. The dots represent the excellent and good cancellations, and the cross marks the poor and bad cancellations. In case of local pattern interference, the poor and bad cancellations should be more frequent in the region of abnormal patterns.

Figure 3 shows the diagrams for anterior (upper left-hand corner) and posterior (upper right-hand corner) myocardial infarct, right and left ventricular strain (right and left center) and right and left bundle branch block (lower right and left corner). In anterior wall infarct, the abnormal pattern (qR, or QR with negative T) appears in the region of V_1 to V_4, and in posterior wall infarct, in the region of L_3, and V or $VI_{5\text{ to }9}$. There is no selective distribution of good or poor cancellations. In substantiation of these scatter diagrams, Fig. 4 shows an excellent cancellation of a large abnormal Q wave in a case of posterior wall myocardial infarct, and Fig. 5 shows the same in two cases of anterior wall myocardial infarct, and in two cases of left ventricular strain.

In right ventricular strain, the strain pattern appears in the region of I to $IV_{10\text{ to }1}$, and in left ventricular strain, in the region of V to $III_{3\text{ to }5}$, (in horizontal hearts). The diagrams do not show any selective distribution of poor cancellations in these regions (Fig. 3).

The lower sections of Fig. 3 show the scatter diagrams in right bundle branch block and left bundle branch block. The regional distribution of typical bundle branch block patterns is similar to that of right and left ventricular strain. Again, there is no selective distribution of good or poor cancellations.*

The absence of regional selective distribution of poor or good cancellations in all categories of patients suggests that the poorer cancellations in patients are not due mainly to interference of local patterns or, more generally, that all categories of pathology affect the cancellation similarly in all directions.

*There was also no selective distribution in patients with emphysema or miscellaneous pathology nor was it expected in these groups.

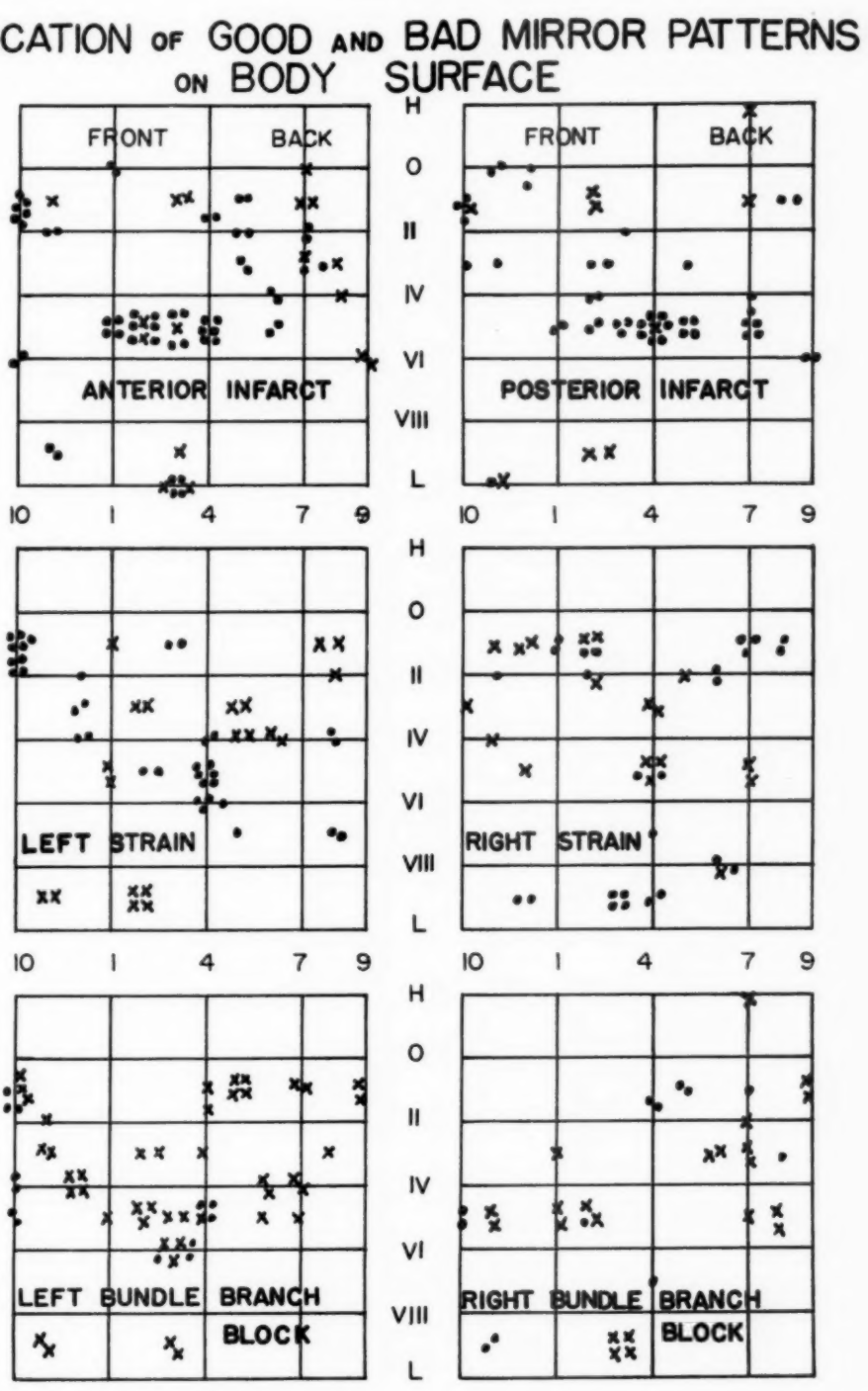

Fig. 3.—Each of the grids represents a map of the body surface, with the Roman numerals indicating horizontal levels (intercostal spaces), and the Arabic numerals vertical divisions (detailed description in text). Dots represent excellent and good cancellations, and crosses represent poor and bad cancellations.

The group of emphysema patients was included for another reason. Emphysema, as such, does not produce any specific type of abnormal pattern. In uncomplicated emphysema the electrocardiogram is "normal" on the basis of conventional standards, although there is a definite shift in the distribution of pattern on the whole surface of the chest.[6] Emphysema was of interest because the volume relationship and positional relationship between heart and lungs are changed. Since the lung is a poor electrical conductor surrounding the heart, it was expected that there might be a change of the cancellation point at the bridge (per cent dial reading), although not necessarily of the cancellation coefficient, the more so, as the electrical structure of the lung tissue is probably changed too. However, there was no significant difference in the dial readings at the cancellation between normal subjects and patients with emphysema. This implies that the relationship of QRS amplitudes at opposite points (location of mirror patterns) is not essentially changed in emphysema.

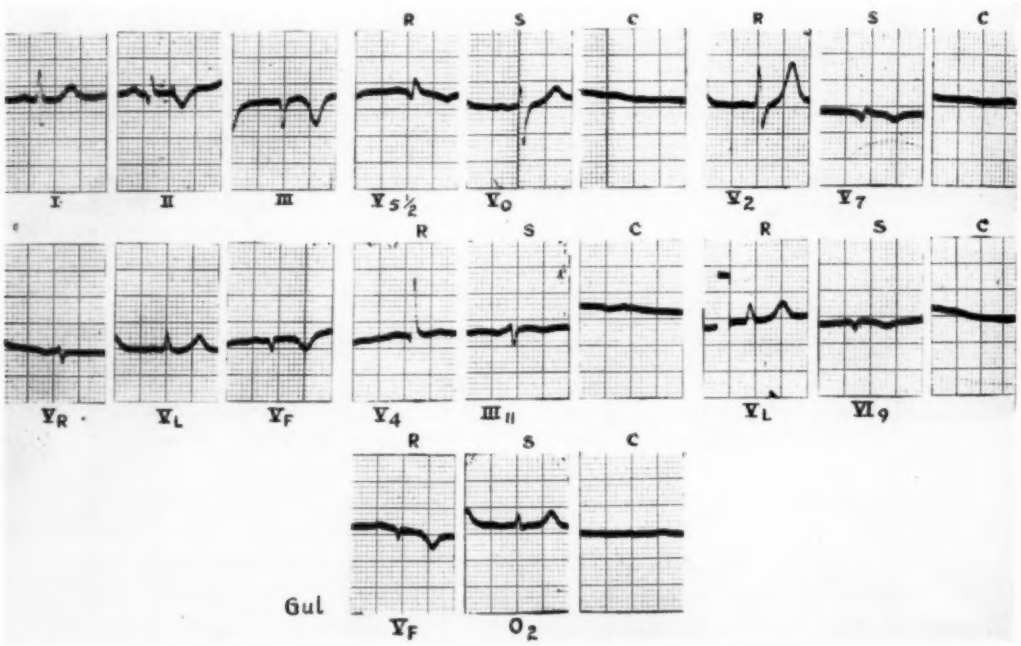

Fig. 4.—Cancellations of the QRS complex in a patient with posterior wall myocardial infarct. Leads II, III and V_F show the typical pattern for this lesion. *R* means pattern at the reference electrode, *S* means pattern at the search electrode, and *C* the resulting cancellation. Location of the electrode is indicated below each record. The abnormal patterns (QS with negative T in V_F, lower row; QR with negative T in $V\,5\frac{1}{2}$, upper row, center) are nearly completely cancelled at the opposite anatomic points (cancellation coefficient < 0.07), but also the cancellation of other reference locations (V_2, V_4, V_L) as well as that of the T wave is very good.

COMMENT

The results show, in general, that the dipole theory is a workable concept for interpretation of electrocardiograms in patients as well as in normal subjects. The cancellation in patients is somewhat poorer on the average, but this can be

reasonably accounted for by experimental limitations or a mobile dipole in bundle branch block. Most important, the poorer cancellation in patients cannot be explained by interference from local patterns. We do not imply that such interference does not exist, it may have been, in fact, a contributing though minor factor in our series. Of much greater importance is the excellent cancellation of abnormal Q waves which was, as a rule, obtained in patients with myocardial infarct. This is not compatible with the "window" theory, that a Q wave represents cavity potentials recorded through the inert infarcted area. It is inconceivable that the opposite ventricular wall always compensates electrically for

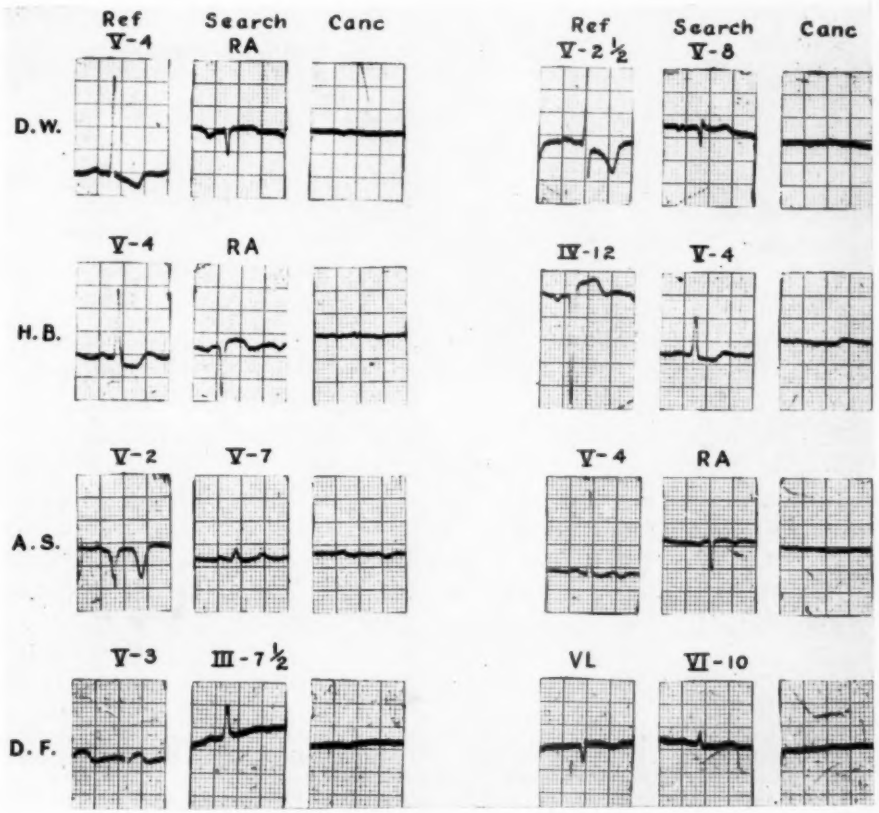

Fig. 5.—Cancellations of the QRS complex in two patients with left ventricular strain (*D. W.* · *H. B.*) and in two patients with anterior-lateral myocardial infarct (*A. S., D. F.*). The typical left ventricular strain patterns in the typical location V_4 are nearly completely cancelled at the opposite point *RA* in both patients *D. W.* and *H. B.*, but also the cancellations at other reference locations are excellent. The residual potential for IV_{12} in *H. B.* is the T wave, for which no optimum cancellation was tried. The abnormal QS patterns in V_2 and V_3 in anterior-lateral infarct are nearly completely cancelled, the residual potentials being the P and T wave in *A. S.* and the T wave in *D. F.* Excellent cancellation is also obtained in V_4 (*A. S.*) and V_L (*D. F.*).

the abnormal Q and the inverted T wave, wherever the Q wave appears. It must be concluded that such a major lesion as a myocardial infarct changes the stereovectorcardiogram as a whole, by a shift of the balance of electrical forces.

In other words, the electrocardiogram recorded at opposite points of the lesion is just as abnormal as the infarct pattern recorded near the lesion. This does not change the localization of lesions, since lesions in different parts of the heart will change the balance of electrical forces in a different and specific way. It changes, however, the interpretation, such as "electrical window," or "intrinsicoid deflection." In general, the results are not compatible with the so-called "unipolar electrocardiography" as a synthesis of local patterns.

SUMMARY

1. The distribution curve of 142 cancellations in thirty-seven patients is similar to that of 106 cancellations in seventeen normal subjects, but the number of good and excellent cancellations in patients is smaller and that of poor and bad cancellations is greater.

2. The significantly poorer cancellation in patients with bundle branch block is explained with a mobile dipole.

3. In patients with right or left ventricular strain, the significantly poorer average cancellation is probably due in large part to technical limitations, but excellent cancellations were also frequently obtained.

4. In patients with anterior or posterior myocardial infarct, the average cancellation coefficient is the same as in normal subjects.

5. There is no significant difference in the cancellation coefficient or the dial reading at the bridge between patients with pulmonary emphysema and normal subjects.

6. The regional distribution of good or poor cancellations over the surface of the body does not show any selective pattern in any category of pathology.

7. There is no evidence that the poorer cancellation in some patients is due to the interference of local patterns.

8. It is concluded that the dipole theory is a valid, workable concept for electrocardiographic interpretation of patients as well as normal subjects.

9. Implications to electrocardiographic theory are discussed.

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THE EFFECT OF EXERCISE ON THE ELECTROCARDIOGRAM OF BUNDLE BRANCH BLOCK

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THE diagnostic value of the electrocardiogram recorded after induced coronary artery insufficiency in patients with arteriosclerotic heart disease has been established. The technique of Master,[1] employing the moderate exercise of the two-step test, is now widely used. It is a safe method, and the results are helpful in establishing the presence of arteriosclerotic heart disease with coronary insufficiency in doubtful diagnostic problems. Likewise, the "Anoxemia Test" of Levy and associates[2] is a valuable method though less widely used.

Diagnostic criteria have been established by Master as follows: "(1) using the P-R interval of the electrocardiogram as the control or isoelectric level, depression greater than 0.5 mm. of the RS-T segment below this level in any lead, (2) a change from an upright T wave to an isoelectric (flat) or inverted T wave, or a change from a negative to a positive T wave (with the exception of Lead III), (3) premature beats or more significant arrhythmias, widening of the QRS, large Q waves, prolongation of the P-R interval, and heart block." Master also stated that the "two-step" exercise test is of value chiefly when the resting electrocardiogram is normal. "Obviously, if this electrocardiogram is abnormal an exercise test is unnecessary." Bundle branch block may be present in the resting electrocardiogram, and the question may arise as to whether or not the patient's symptoms are due to arteriosclerotic heart disease. Is the bundle branch block (usually right) of the benign type and without serious significance?

There is little reference to the effect of exercise on the electrocardiogram of bundle branch block, either in the normal person or in the patient during angina of exercise or of anoxemia. Several observers have published records of bundle branch block occurring during anginal seizures. Bousfield[3] reported a case of syphilitic aortitis in which during a short anginal attack right bundle branch block occurred, but disappeared with cessation of the pain. Arrilaga[4] said that during pain bundle branch block was observed which disappeared when the pain ceased. Twiss and Sokolow[5] also demonstrated the appearance of bundle branch block in a positive test. Parkinson and Bedford[6] published an electrocardiogram of right bundle branch block (in a case of old posterior infarction). The electrocardiographic evidence of the posterior infarction was augmented during the pain. Levy and associates[2] published an electrocardiogram made during an

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anoxemia test of a patient with right bundle branch block. The test was positive, showing striking depression of the S-T segment in Lead IV. Post-mortem examination showed narrowing of the left circumflex artery and widespread fibrosis of the posterior wall of the left ventricle. While these records have been presented and described, there has been no systematic study as to the effect of exercise or of anoxemia on the electrocardiogram of bundle branch block.

The present study was undertaken to evaluate the exercise test in patients who exhibit bundle branch block in the control electrocardiogram.

METHOD

In patients whose electrocardiograms demonstrated bundle branch block, a random selection for study was made without regard for the presence or absence of clinical evidence of heart disease. These patients were not hospital cases. In most instances the Master "two-step" technique[1] was employed, although in a few cases a lesser degree of exercise was used. Complete control electrocardiographic studies were performed in the recumbent posture with the patient at rest. The patients were then exercised to a prescribed degree, immediately following which the electrocardiogram was repeated. During the rest period the electrocardiogram was again taken at intervals of two to ten minutes. Usually the standard limb leads and V_2, V_4, and V_6 were taken after the exercise, although in some instances the augmented limb leads and one apical precordial lead were used.

Patients receiving digitalis preparations were excluded from the study in view of the known effect of digitalis in exercise.[7]

Two cases were excluded from this study because their electrocardiograms at rest were within normal limits, but showed bundle branch block on exercise only. Although both of these patients showed abnormal responses, in this study we were concerned only with patients showing bundle branch block in the control electrocardiogram at rest.

RESULTS

A total of fifty-six patients were studied. Of these the electrocardiograms at rest exhibited the following: right bundle branch block in twenty-seven patients, incomplete right bundle branch block in six, left bundle branch block in twenty, and Wolff-Parkinson-White syndrome in three subjects.

Right Bundle Branch Block.—Of the twenty-seven patients tested only four showed a positive test. The results are shown in Table I. Of the four patients with positive tests one had definite arteriosclerotic heart disease with angina pectoris (Fig. 1), one had hypertensive cardiovascular disease with early failure, one had gout and obesity, and the other a labile hypertension and alcoholism.

Negative tests occurred in six patients with arteriosclerotic heart disease and in six others with hypertensive cardiovascular disease, as well as in eleven otherwise normal persons. Figure 2 shows a negative test in a patient with definite angina pectoris.

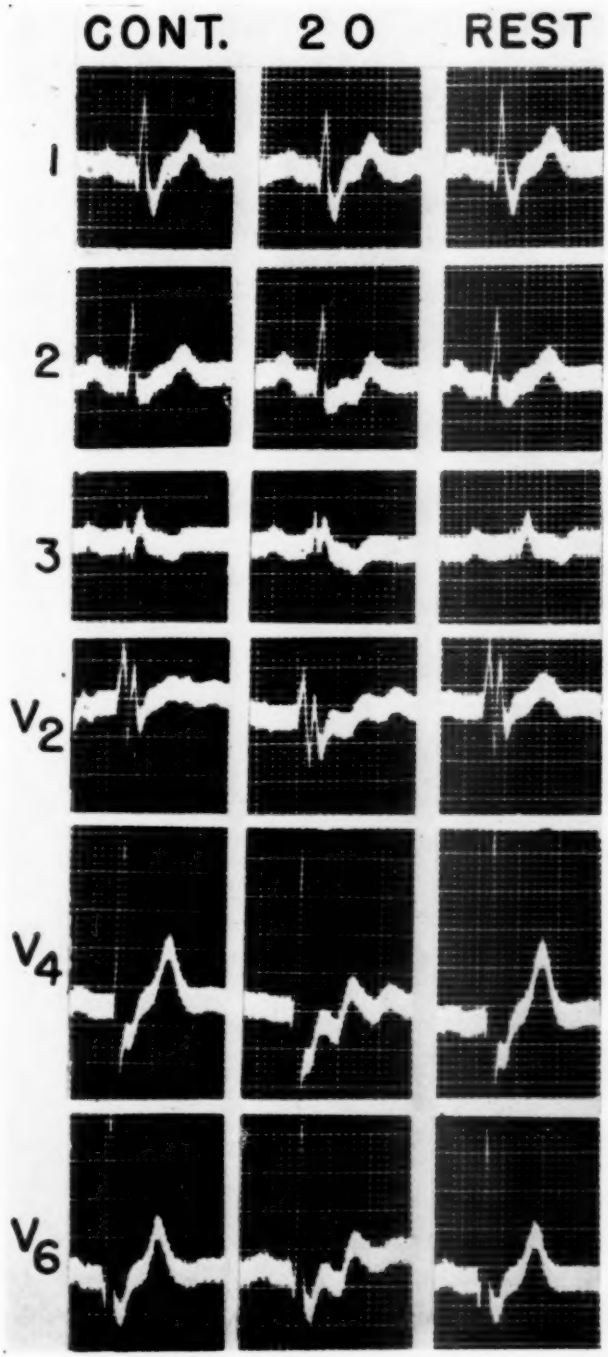

Fig. 1.—Positive exercise test in patient with right bundle branch block and definite angina pectoris. Shown are Leads I, II, III, V_2, V_4, and V_6 during control period (*cont.*), immediately following 20 ascents (*20*) and after six minutes rest.

Incomplete Right Bundle Branch Block.—Of the six patients in this group the test was positive in one, a patient with arteriosclerotic heart disease and hypertensive cardiovascular disease. The five negative tests were in patients without clinical evidence of heart disease.

Left Bundle Branch Block.—Of the twenty patients in this group seven showed positive tests,* while thirteen gave negative tests. The results are shown in Table II. The test was positive in four patients with definite arteriosclerotic heart disease. Of the other three positive patients one (the patient with incomplete left bundle branch block) had probable arteriosclerotic heart disease, one had hypertensive cardiovascular disease, and one (76 years of age) had no definite

TABLE I. EFFECT OF EXERCISE IN TWENTY-SEVEN PATIENTS WITH RIGHT BUNDLE BRANCH BLOCK

A. Positive Test (Four Patients)

PATIENT	AGE	BLOOD PRESSURE	HISTORY OF INFARCTION	DIAGNOSIS	EXERCISE (TRIPS)	REMARKS
1.	45	120/80	0	Gout, obesity	25	Marked T-wave inversion in V_4.
2.	62	160/70	0	ASHD	20	S-T segment and T-wave inversion in all leads.
3.	62	190/90	0	HCVD, early failure	15	T in V_5 from deeply inverted to diphasic.
4.	42	154/90	0	Labile hypertension, alcoholism	15	T in V_4 from inverted to flat.

B. Negative Test (Twenty-three Patients)

1.	70	120/80	0	ASHD	50	
2.	57	150/100	Posterior	ASHD	12 sit-ups	
3.	47	150/100	0	ASHD	15	
4.	60	130/80	0	ASHD	10	
5.	63	150/90	0	ASHD	15	
6.	65	150/90	0	ASHD	40	
7.	45	154/90	0	HCVD	10	
8.	62	164/120	0	HCVD	10	
9.	53	180/120	0	HCVD, Aortic stenosis	15	
10.	43	160/110	0	HCVD	15	
11.	56	180/130	0	HCVD	15	
12.	73	170/100	0	HCVD	25	
13.	52	130/90	0	Diabetes	10	
14.	47	130/90	0	Hiatus hernia	15	
15.	47	152/90	0	Normal	10	
16.	46	132/80	0	Normal	38	
17.	59	140/90	0	Normal	18	
18.	46	130/90	0	Normal	10	
19.	47	120/80	0	Normal	10	
20.	45	120/80	0	Normal	40	
21.	39	110/80	0	Normal	30	
22.	37	120/70	0	Anxiety	40	
23.	50	120/80	0	Normal	15	

ASHD = arteriosclerotic heart disease
HCVD = hypertensive cardiovascular disease

*One of these cases was considered to have incomplete left bundle branch block.

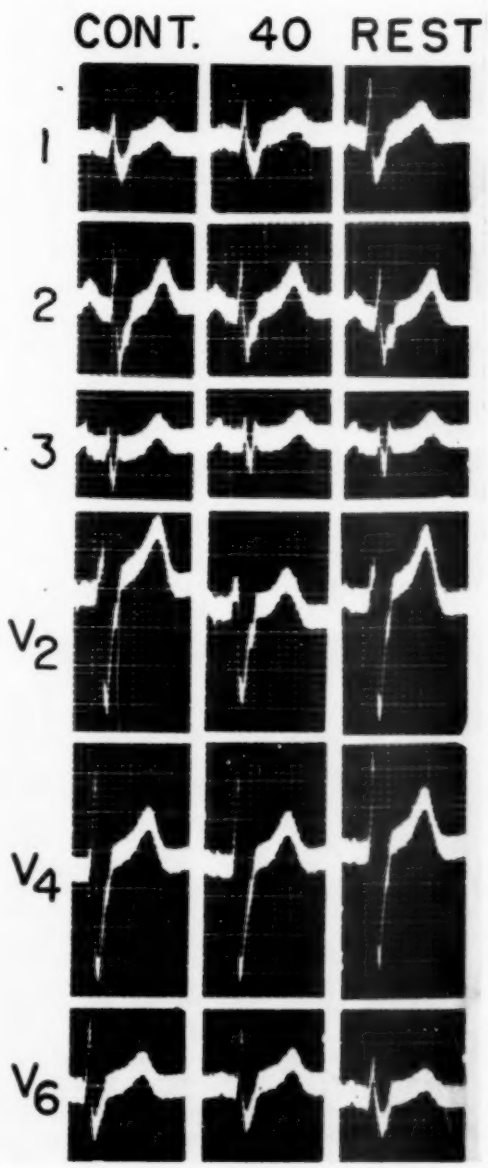

Fig. 2.—Negative exercise test in a patient with right bundle branch block and definite angina pectoris. Shown are Leads I, II, III, V_2, V_4, and V_6 during control period (*cont.*), after a total of 40 ascents (*40*) and after five minutes rest.

clinical coronary insufficiency. Negative tests occurred in five patients with definite arteriosclerotic heart disease (most of whom also had hypertension) and in six patients with hypertensive cardiovascular disease. The other two negative patients were one with rheumatic mitral insufficiency and a normal woman. Figures 3 and 4 demonstrate exercise tests in patients with definite angina pectoris. Both tests are borderline but suggestive.

Summary of Results in Complete Bundle Branch Block

	Positive Test	Negative Test
Rt. B.B.B.	4	23 (6 with clinical diag. of A.S.H.D.)
Lt. B.B.B.	7	13 (5 with clinical diag. of A.S.H.D.)

Comparing right with left bundle branch block, it can be seen that there is no significant difference in the incidence of positive versus negative tests in the presence of arteriosclerotic heart disease.

Wolff-Parkinson-White Syndrome.—Of the three patients in this group only one had a history suggestive of coronary insufficiency; however, the exercise test was considered positive in all three. Each patient showed a change in the direction of the T wave in the precordial lead. Figure 5 shows a positive test in a 50-year-old patient with probable coronary insufficiency.

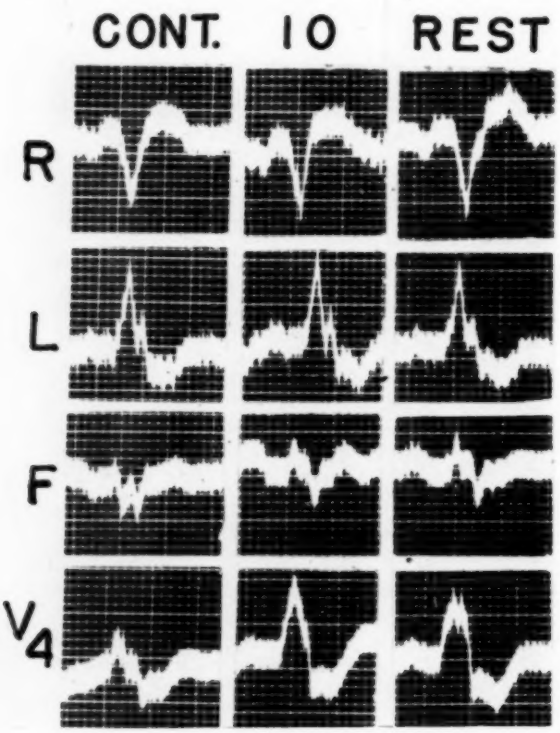

Fig. 3.—Exercise test in a patient with left bundle branch block and definite angina pectoris. Shown are Leads aV_R (*R*), aV_L (*L*), and aV_F (*F*), and V_4 during control period (*cont.*), after 10 ascents (*10*) and after five minutes rest.

TABLE II. EFFECT OF EXERCISE IN TWENTY PATIENTS WITH LEFT BUNDLE BRANCH BLOCK

A. Positive Test (Seven Patients)

PATIENT	AGE	BLOOD PRESSURE	HISTORY OF INFARCTION	DIAGNOSIS	EXERCISE (TRIPS)	REMARKS
1.	56	140/100	0	ASHD	5	T in V_4 diphasic to upright.
2.	59	150/90	Probable	ASHD	20	Depress. S-T in V_4.
3.	66	200/130	0	ASHD	10	Depress. S-T in V_4.
4.	57	174/90	0	ASHD	10	Depress. S-T in V_4.
5.	56	140/90	Possible old	Probable ASHD, gall bladder disease	6	Incomplete LBBB, T wave flat in V_4 from upright.
6.	76	160/90	0	Normal	10	Depress. S-T in V_4.
7.	51	190/130	0	HCVD	15	Freq. Pr. Beats S-T depress. in V_4.

B. Negative Test (Thirteen Patients)

1.	52	150/59	0	ASHD	17	
2.	51	170/110	Probable	ASHD	17	
3.	69	200/110	0	ASHD	15	
4.	62	120/74	Posterior	ASHD	10	Stopped by pain
5.	55	172/90	0	ASHD (gallop rhythm)	15	
6.	54	150/120	0	HCVD	10	Sit-ups
7.	61	170/90	0	HCVD	15	
8.	59	180/110	0	HCVD	15	
9.	46	160/100	0	HCVD	38	
10.	53	160/100	0	HCVD	10	
11.	55	170/110	0	HCVD	20	
12.	51	140/90	0	Rheumatic M. I.	15	
13.	60	160/90	0	Normal	0	

ASHD = arteriosclerotic heart disease
HCVD = hypertensive cardiovascular disease
M.I. = Mitral Insufficiency

DISCUSSION

Although it is frequently stated that the exercise or anoxemia tests should not be done in the presence of bundle branch block,[8] we believe the test does have value in the elucidation of evidence of coronary insufficiency. Certainly, the presence of bundle branch block in itself does not necessarily constitute coronary insufficiency or even myocardial disease. Recent studies have emphasized that the electrocardiographic pattern of either right or left bundle branch block does not, per se, permit a prognosis.[9-11] As a matter of fact, there may be no evidence of heart disease in a large percentage, especially those with right bundle branch block[12] and in the younger age groups.[13]

In this series left bundle branch block is much more frequently associated with significant heart disease than is right bundle branch block. Of the twenty patients with left bundle branch block all but one had clinical evidence of heart disease. Of the twenty-seven patients with right bundle branch block eleven were patients with no evidence of clinical heart disease. Two of the positive tests in right bundle branch block were in patients with no definite evidence of heart disease. Likewise, in the three cases of Wolff-Parkinson-White syndrome the test was positive in each, despite the absence of clinical heart disease in two. Similar changes have been found by others in Wolff-Parkinson-White syndrome;[14] the cause thereof is not understood.

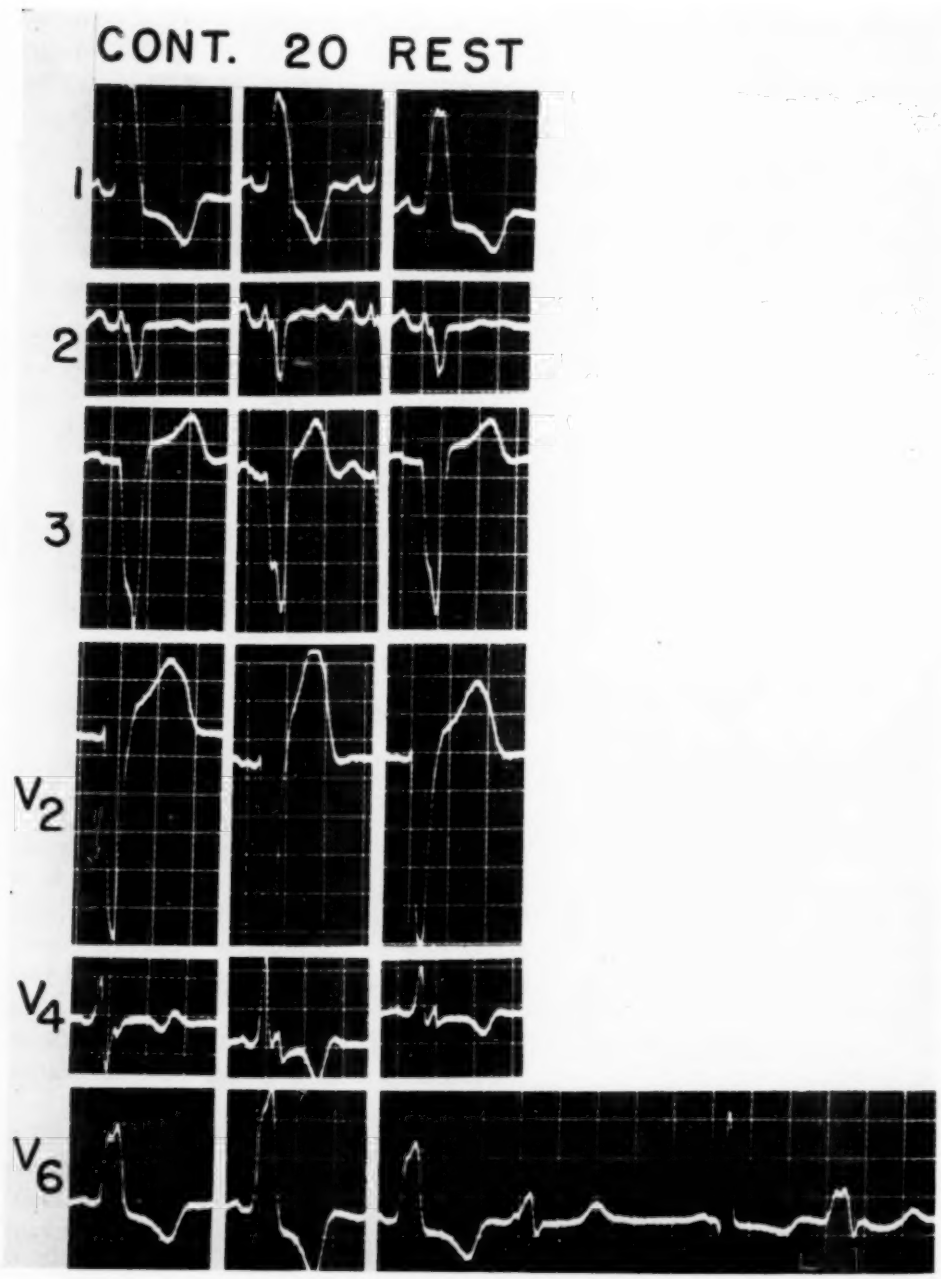

Fig. 4.—Equivocal exercise test in a patient with left bundle branch block and definite angina pectoris.

The incidence of positive tests in coronary insufficiency in the presence of bundle branch block is not significantly different from that reported by various investigators, in which the control electrocardiogram showed relatively normal intraventricular conduction. Table III is a compilation of the incidence of positive tests found in patients with clinical coronary insufficiency as reported by various authors.

Since the electrocardiogram may be considered as the summation of the dextro- and levocardiograms[26] in bundle branch block, the asynchronism between the dextro- and levocardiograms accounts for the altered configuration of the QRS complexes and the S-T-T components. However, despite the abnormal spread of the excitatory process, induced coronary insufficiency, presumably by primarily altering the levocardiogram, may produce changes even in the presence of bundle branch block. The occurrence of positive tests in left bundle branch block as well as in right bundle branch block would indicate that subendocardial ischemia can still be manifested despite aberrant activation and repolarization of the left ventricle.

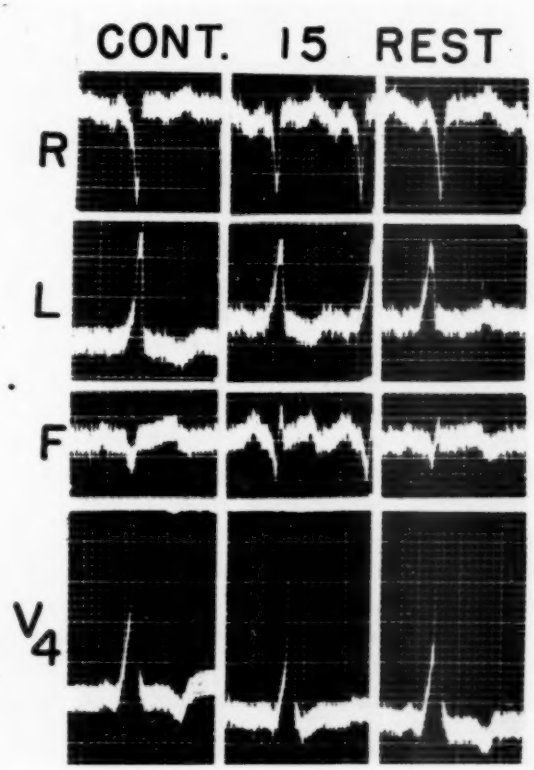

Fig. 5.—Positive exercise test in a patient with Wolff-Parkinson-White syndrome and symptoms of coronary insufficiency.

TABLE III. REPORTED INCIDENCE OF POSITIVE ELECTROCARDIOGRAPHIC TESTS FOLLOWING INDUCED CORONARY INSUFFICIENCY

AUTHOR	METHOD OF EXAMINATION	DIAGNOSIS	TOTAL PATIENTS	POSITIVE (%)
Siegel & Feil (1931)	During anginal attack	ASHD	11	72.5
Wood & Wolferth (1931)	Exercise	Angina	24	50
Riseman et al. (1940)	Exercise	Angina	15	73.5
Evans & Bourne (1941)	Exercise	Angina	20	45
Twiss & Sokolow (1942)	Max. 2-step	Angina	66	56
Master et al. (1942)	Standard 2-step	Angina & old coronary	136	33
	Double standard	Angina & old coronary	78	43.6
Unterman & De Graff (1948)	Exercise	Typical & questionable angina	52	38.4
Wood et al. (1950)	Max. exercise	Angina	100	88
Larsen (1938)	10% O_2	ASHD	17	77
Levy et al. (1941)	10% O_2	ASHD	95	48
Patterson et al. (1942)	10% O_2	ASHD	157	49
Pruitt et al. (1945)	10% O_2	ASHD	92	53
Biörck (1946)	10% O_2	ASHD	66	33

ASHD = arteriosclerotic heart disease
HCVD = hypertensive cardiovascular disease

SUMMARY

A systematic study was undertaken to determine the effect of the exercise test on the electrocardiogram of fifty-six patients with bundle branch block. Of twenty-seven patients with right bundle branch block, four showed a positive test; only two of the four positive reactors had definite evidence of heart disease, while six patients with arteriosclerotic heart disease had negative tests. Of six patients with incomplete right bundle branch block only one had arteriosclerotic heart disease and the exercise test was positive in this case. Of twenty patients with left bundle branch block seven showed positive tests, while five others with arteriosclerotic heart disease had negative tests. All three patients with Wolff-Parkinson-White syndrome had positive tests, despite the absence of other clinical evidence of heart disease in two.

The exercise test was positive in approximately 50 per cent of patients with arteriosclerotic heart disease and complete bundle branch block. Presumably false positives occurred in two patients with right bundle branch block and in two with the Wolff-Parkinson-White syndrome, indicating a possible hazard in the evaluation of the effect of exercise in the presence of aberrant conduction.

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THE EFFECT OF MODERATE AND HARD MUSCULAR WORK ON THE SPATIAL ELECTROCARDIOGRAM

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IN SPITE of the extensive literature on the electrocardiographic response to exercise, recently reviewed by Scherf and Schaffer,[1] basic information is still missing. Much of the published material is concerned with the application of exercise tolerance tests to patients with suspected or diagnosed coronary disease. In most of these tests no attempt is made to correlate the electrocardiographic changes with the physiologic load. Scherf and Schaffer go so far as to claim that the type or amount of exercise is not important for the diagnostic value of the test. This implies a critical rather than a quantitative response. While this is not impossible, it has not yet been proved to be the case.

There is ample evidence that the physiologic stress is different in aerobic work, performed at a steady state of respiratory and circulatory functions, and in anaerobic work with the oxygen demand exceeding the maximum oxygen intake.[2-4] In aerobic work the physiologic load is largely defined by the oxygen intake, while in anaerobic work, which can be maintained only for a few minutes, the ability to accumulate a maximum oxygen debt is of importance, although other factors are also involved.[5] It would be of interest to know whether the electrocardiographic changes are similar or different in these types of physiologic stress.

The exercise tests commonly used in electrocardiography, such as the two-step test,[6] genuflections, or stair climbing, are probably mixed types of aerobic-anaerobic work and, therefore, the least suitable for a testing procedure. They are erroneously termed[1] moderate because the duration is short. It is unlikely that a steady state is reached in many patients and possibly even in some normal subjects. It is possible, therefore, that different types of physiologic load are compared in patients and in normal controls with the "two step" test or similar types of exercise. The selection of the type of exercise for electrocardiographic tolerance tests so far has ignored the experience in testing of physical fitness.[4]

It was felt that, as a basis for interpretation of the electrocardiographic response to exercise, the changes produced by moderate aerobic work, heavy aerobic

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work, and anaerobic work should be compared. Occasionally, some experiments were performed with one or the other of these types of exercise,[7] but no systematic comparison in the same subjects has been reported.

The analysis of electrocardiographic changes has been essentially limited to a qualitative or, at best, semiquantitative evaluation of the S-T segment and T-wave changes. Changes of the QRS complex, although noted,[8,9] were either not consistent or prominent enough to serve as a diagnostic criterion. It is possible that the failure of the QRS complex to show significant changes results from the limitation to the scalar electrocardiogram. Scherf and Schaffer[1] state: "The effect of exercise on the magnitude, form, irregularities, and position of the spatial vector loops of the QRS complex is not known." It may be added also that the spatial orientation of T-wave changes has not yet been studied.

It has been attempted in this study to provide information about the changes of spatial QRS and T vectors in three basic types of exercise.

METHOD

Walking and running on the motor-driven treadmill were investigated at the following combinations of speed (miles per hour), grade (per cent), and duration (minutes): walking—15 minutes at 3 m. p. h. and 0 per cent, 5 per cent, and 10 per cent grades; running—6 m. p. h. at 0 per cent grade for 3 minutes and at 0 per cent grade for 30 minutes, 8 m. p. h. at 0 per cent grade for 1.5 and 3 minutes and at 10 per cent grade for 1 minute.

The experiments were performed in six normal young men in good physical condition, but not especially trained. The three variations of walking, running at 8 m. p. h., 0 per cent grade, for 3 minutes were studied in all subjects, running at 6 m. p. h. for 30 minutes in five subjects, and the other variations in two or three subjects.

Electrocardiograms were taken in supine position before and immediately (30 to 60 seconds) after the exercise. In addition to the standard leads six to eight precordial leads were taken at the fifth intercostal space so as to include the transitional zone of the T wave. The analysis of the mean spatial QRS and T vectors was made by means of a newly developed method[10] based on the determination of the direction of the vectors in the horizontal plane from the precordial leads and of the direction and magnitude in a frontal plane from Leads I and III. The vectors are given in terms of a horizontal angle (H degrees), which corresponds to the azimuth, a vertical angle (V degrees), and magnitude (Mag.) in millimeter standardized deflection (1 mm. = 0.1 mV). The angle between spatial vectors is also measured. The 0°–180° reference line for the horizontal angle is a transverse line, parallel to Lead I, passing through a hypothetical center of the heart from the left side (0°) to the right (± 180°), with the positive hemisphere in front and the negative hemisphere in the back. The vertical angle V° is the angle between the vector and a vertical projection through the hypothetical center of the heart onto the horizontal plane. The elevation in analytical geometry is 90–V°. The reason for the definition of V° is simplicity of measurement and avoidance of negative values for V°. The angle between spatial vectors (dA°) is positive when the rotation from the first to the second vector, in their

sequence in the cycle, is in clockwise rotation as viewed from above. The plane which includes the mean QRS and T vector was measured by means of a device supplementary to the spatial vector analyzer.[11]

The S-T segment was measured in Lead II, but the vector was not determined. While the deviations of the S-T segment after exercise may be sufficiently large to be measured as spatial vectors, the small deviations and the wide transitional zone in resting condition make any definition of S-T vectors at rest very uncertain.

Because of the small number of subjects no statistical evaluation of significance was made. However, in case of a uniform response in all subjects statistical significance seems to be fairly certain (** in Table I) and probable (* in Table I) in case of a uniform response in all subjects but one.

RESULTS

The main results are summarized in Table I. Three basic types of exercise are compared: moderate aerobic (walking at 3 m.p.h., 5 per cent grade for 15 minutes); hard aerobic (running at 6 m.p.h., horizontal, for 30 minutes); and anaerobic work (running at 8 m.p.h., horizontal, for 3 minutes).

No significant differentiation of the electrocardiographic response in the three variations of walking was observed; therefore, the variation (3 m.p.h., 5 per cent grade) in Table I is representative for walking at moderate speed in general. The oxygen consumption in walking, per kilogram of body weight, can be predicted with fair accuracy.[12] The excess oxygen consumption (above the basal metabolic rate) at 3 m.p.h., horizontal, 5 per cent grade, and 10 per cent grade equals on the average ±6 c.c., 11 c.c., and 18 c.c. per kilogram of body weight, respectively. It is of interest that within that range an increase of the excess oxygen by about three times does not produce significant differences in the electrocardiographic response.

Running for thirty minutes at 6 m.p.h. is hard aerobic work very close to the maximum oxygen intake.[13] The third type of exercise, running at 8 m.p.h., was definitely anaerobic. None of the subjects could have continued this rate after three minutes for more than a few seconds. Raising the grade to ten per cent decreased the endurance to about one and one-half minutes.

Table I shows that exercise changes not only the T vector but also the QRS vector. The response to the different types of exercise shows definite differences. Only in anaerobic work are noted a significant decrease of the magnitude and a significant shift of H° (to the back) of the QRS vector. The vertical angle V° of the QRS vector decreases significantly in all types, most in severe aerobic work, least in moderate aerobic work. This means that the direction is more vertical downward.

The magnitude of the T vector increases in severe aerobic work but decreases slightly in the other two types of exercise. The horizontal angle H° shifts to the right in the anaerobic and more so in the severe aerobic work, in contrast to the shift to the left in moderate aerobic work. The vertical angle shows no significant change in severe aerobic work, and a significant decrease in anaerobic work.

TABLE I. AVERAGE CHANGE OF MEAN SPATIAL QRS AND T VECTORS IN THREE BASIC TYPES OF EXERCISE (MODERATE AEROBIC, HARD AEROBIC, ANAEROBIC)

CONDITIONS OF WORK	SUBJECT NO.	QRS VECTOR			T VECTOR			dA°	QRS-T PLANE		S-T_2
		H°	V°	MAG	H°	V°	MAG		H°	V°	
Rest	6	−22.5	18.3	15.7	47.8	59.2	4.6	56.7	30.6	105.2	+0.3
3 m.p.h. 5%, 15 min.	6	−1.33	−4.33**	−0.58	−1.83*	− 6.68*	−0.55*	− 6.50**	+1.50	−1.33*	−0.3**
8 m.p.h., 0%, 3 min.	6	−9.0*	−6.17**	−2.18**	+12.33**	−10.00**	−0.17*	− 4.0	+ 6.0*	−5.33**	−1.34**
6 m.p.h., 0%, 30 min.	5	−0.2	−9.8*	+0.7	+27.5**	+ 7.5	+3.3**	+10.0*	+18.0**	−8.3*	−1.70**

H° = horizontal angle, V° = vertical angle, Mag = magnitude, dA° = angle between spatial vectors.
**Uniform response in all subjects.
*Uniform response in all but one subject.

The spatial angle dA° between the mean QRS and T vectors increases significantly in severe aerobic work but decreases in moderate aerobic work. An increase of the spatial angle has been recognized as a typical feature of ventricular ischemia;[14] that this change occurs only in severe aerobic work in normal young men is of great interest. The change in the orientation of the plane, which includes the mean QRS and T vector, and the change of the S-T segment are in the same direction in all types of work with the greatest changes in the severe aerobic type of work.

DISCUSSION

Comparison of the response in the three basic types of exercise reveals characteristic differences, which are not surprising in view of the different physiologic load. This means that the type of exercise is not irrelevant for the application of exercise tests in clinical electrocardiography. The following items show significant changes in all three types of work: QRS-V°, T-H°, T-Magnitude, QRS-T plane-V°, and S-T_2. In all these items the change, ignoring its direction, is greatest in the severe aerobic work (6 m.p.h., 30 min.). It seems safe to assume that this type of work is, so far as the heart is concerned, a more severe stress than anaerobic work. This conclusion conforms to the general concept derived from studies of respiratory exchange and hemodynamics.[2,3]

The shift of the horizontal angle H° of the T vector to the right and the increase of dA° and of the S-T depression suggest left ventricular ischemia as the main underlying factor in severe aerobic work. The increase of the magnitude of the T vector may also be due to ventricular ischemia. Increase of the T vector is known in acute coronary insufficiency of the subendocardial ischemia type,[15,16] although no quantitative information is yet available. The decrease of the magnitude of the T vector in moderate aerobic work, in contrast to the increase in severe aerobic work, might suggest that the decrease is typical for an adaptation process,[17] and that the increase is typical for stress or fatigue. Schlomka[8] found that fifty genuflections decreased the T wave in normal young men in good condition of physical fitness (Group A) and increased it in normal men in a poorer state of physical fitness (Group B). The physical fitness was not actually determined, but Group A showed faster recovery of pulse rate, blood pressure, and electrocardiographic changes after the exercise. A differentiation of the response after the same type of exercise between individuals in a different state of physical fitness is comparable to the response to different severity of exercise in the same subjects. Schlomka used only one chest lead, but unfortunately the location of the electrodes was not precisely stated. The QRS complex was mainly positive or equiphasic of the RS type, and T was positive. Therefore, no differentiation between change of the magnitude and change of the direction of the T vector could be made. The number of subjects was not given, and no statistical evaluation was made.

In spite of these defects in Schlomka's work, there was probably some differentiation in the response of the T amplitude between subjects of different physical fitness in the line of our observations.

The increase of T-Magnitude in severe aerobic work, as contrasted to the decrease in moderate work, may be due to two factors: increased severity (level of

O_2 transport) and duration (fatigue). In three subjects the same speed (6 m.p.h.) and grade (horizontal) were compared at three minutes and thirty minutes duration of work. The mean change of T-Magnitude after three minutes work was −0.2 but not uniform in the three subjects. However, all three subjects responded with an increase of T-Magnitude (mean +2.9) when the duration was prolonged to thirty minutes. While no definite statement can be made as to the effect of severity in aerobic exercise of short duration, it seems that the duration plays the most important part for the response in prolonged severe aerobic work. If this is the case, the change of T-Magnitude may be an interesting criterion for clinical application.

In anaerobic work the decrease of the magnitude of the QRS vector (QRS-Mag) is far greater than the change of T-Magnitude. According to our experience the level of the maximum oxygen intake is reached in about ninety seconds at 8 m.p.h.[13] If the total duration of 3 minutes is divided into two periods of 1.5 minutes each, the average oxygen intake is much less during the first period. In three subjects the mean decrease of ORS-Magnitude was −2.1 mm. after 1.5 minutes and −2.8 mm. after 3 minutes. Raising the grade in 1.5 minutes anaerobic work (8 m.p.h.) from 0 to 10 per cent changed the mean response of QRS-Magnitude from −1.5 to −2.4 mm. This would be hard to understand if the maximum oxygen intake is a constant for the same individual and the same type of exercise. However, in recent investigations in this laboratory[18] it was shown that the maximum oxygen intake during running is a variable, depending, among other factors, on the grade. The gradation of the response of QRS-Magnitude, therefore, correlates the physiologic load. Since in patients any work tends to be more anaerobic (unless extremely light) than in normal subjects, changes of the QRS vector, which have been more or less ignored so far, may serve as useful diagnostic criteria in exercise tolerance tests.

SUMMARY

1. In six normal young men the effect of three basic types of exercise (moderate aerobic: walking at 3 m.p.h., 5 per cent grade for 15 minutes; anaerobic: running at 8 m.p.h., horizontal, 3 minutes; severe aerobic: running at 6 m.p.h., horizontal, for 30 minutes) on spatial mean QRS and T vectors was investigated.

2. Characteristic differences were obtained in the three different types of exercise. In anaerobic work changes of the horizontal angle and the magnitude of the spatial QRS vector contrast with the absence of such changes in the other types of work.

3. Severe aerobic work is characterized by a large shift of the horizontal angle of the T vector to the right, increase of the spatial angle between the mean QRS and T vector, increase of the magnitude of the T vector, and depression of the S-T segment. These changes can be explained on the basis of left ventricular ischemia. The over-all changes in this type of work exceed those in the two other types of work.

4. It is suggested that the shift to the left of the mean T vector and its decrease in moderate aerobic work are due to adaptation, and the opposite changes in severe aerobic work are due to fatigue.

5. On the basis of the results obtained several suggestions for applications to exercise tests in clinical electrocardiography are made.

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HIGH FIDELITY ELECTROCARDIOGRAPHY: FURTHER STUDIES INCLUDING THE COMPARATIVE PERFORMANCE OF FOUR DIFFERENT ELECTROCARDIOGRAPHS

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THE purpose of this paper is to compare the high fidelity response of four electrocardiographs which have four different types of galvanometers and to discuss certain other aspects of this subject. In a previous paper we reviewed the pertinent literature[1-3] and reported the results of our studies[4] of the standard extremity and precordial leads recorded by the cathode ray oscillograph (hereafter referred to as C.R.O.) and a high speed camera. Records thus obtained are considerably expanded, being approximately six times the amplitude and twelve times the width of conventional records. In such records high frequency components of at least 500 cycles per second and probably more are revealed. This instrument is the criterion for high fidelity response with which the other three electrocardiographs will be compared.

MATERIAL AND METHODS

The standard extremity and precordial leads which had been recorded with the C.R.O. in sixty normal individuals were reviewed for high frequency components of approximately 200 cycles per second or higher. Sixteen leads from fourteen individuals were selected for further study. These leads were selected because each one had one or more clearly identifiable, consistently present, high frequency components which were well suited for this comparative study. One individual with heart disease was also included in this study.

Frequently there are marked irregularities in the speed of the various parts of the deflection in the C.R.O. as manifested by differences in photographic density of the tracing, but these irregularities are hard to compare so we selected phenomena which could be more easily measured, such as distinct notching or beading.

Each lead studied was recorded by the following instruments: the C.R.O. standardized at 1 mv. = from 4 to 7 cm. depending on the size of the deflection, and a paper speed of 350 mm. per second; a new high frequency D'Arsonval type

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(mirror) galvanometer* standardized at 1 mv. = 2 cm. and a paper speed of 75 mm. per second; a direct writing instrument† standardized at 1 mv. = 1.5 cm., and a paper speed of 100 mm. per second; and a string galvanometer standardized at 1 mv. = 1 cm. and a paper speed of 100 mm. per second. In each individual, records were made consecutively within a period of about twenty minutes. The subject was recumbent. The respiratory cycle was taken into account so that all leads compared were recorded at the end of normal quiet expiration.

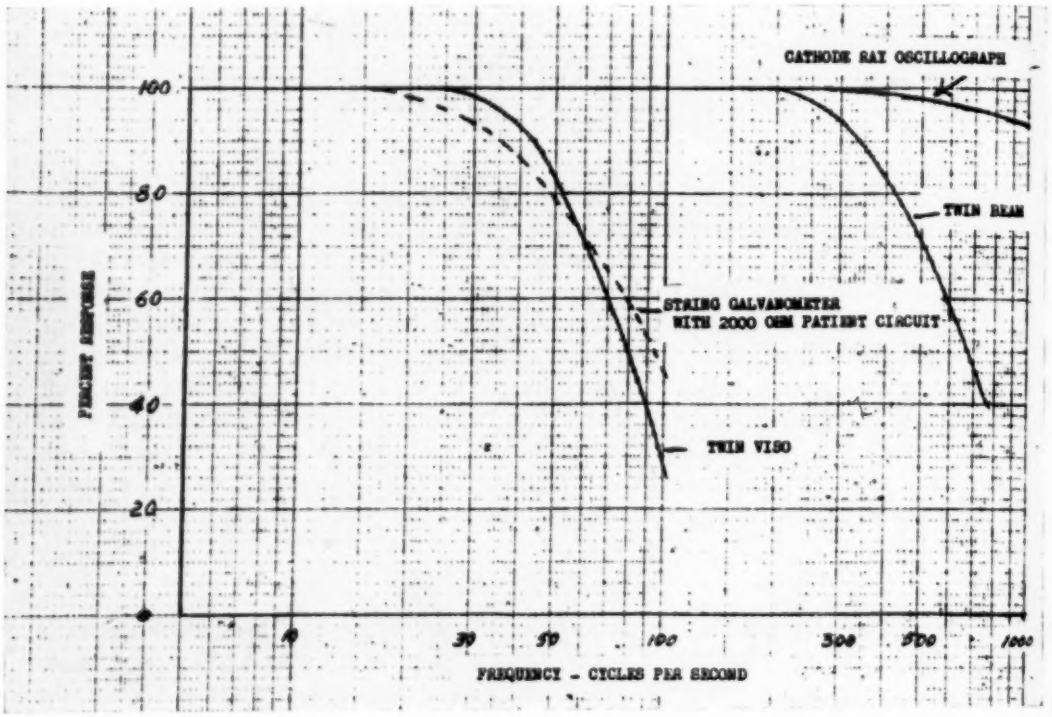


Fig. 1.—Frequency response curve of the instruments used in this study.

RESULTS

In all sixteen leads the well defined high frequency phenomena of the C.R.O. records selected for study were also visible in records made by the high frequency mirror galvanometer but were not visible in records made by the direct writer or the string galvanometer. This was to be expected since the maximum frequency response of the latter two instruments is well below the estimated frequency of the phenomena selected for study. The frequency response curves of these four instruments are shown in Fig. 1.

*Twin-Beam, Sanborn Company. This instrument employs a 500 cycle galvanometer capable of a frequency response much higher than that of other mirror galvanometers commonly used in commercially available electrocardiographs in this country.

†Twin-Viso, Sanborn Company.

The marked irregularities in the density of the photographic trace, so common in the C.R.O. records, were not as readily apparent in the mirror galvonometer records for two reasons. First, some of these differences may be due to the higher frequency response of the C.R.O. Second, the light intensity produced by the excitation of the fluorescent material on the face of the cathode ray tube is increased as the cathode ray beam slows down and vice versa. In addition, the exposure of the photographic films is increased by this slowing down as well as by the greater light intensity, so that the photographic record shows an exaggerated variation in density.

In the case of the mirror galvanometer records, the apparent width of the trace varies inversely with the speed of the spot across the paper. An examination of the comparative records in Figs. 3 and 4 shows that wherever the C.R.O. trace became blacker, the Twin-Beam trace became thicker. With the existing instrumentation it is easier to appreciate these changes in the C.R.O. than in the mirror galvanometer records.

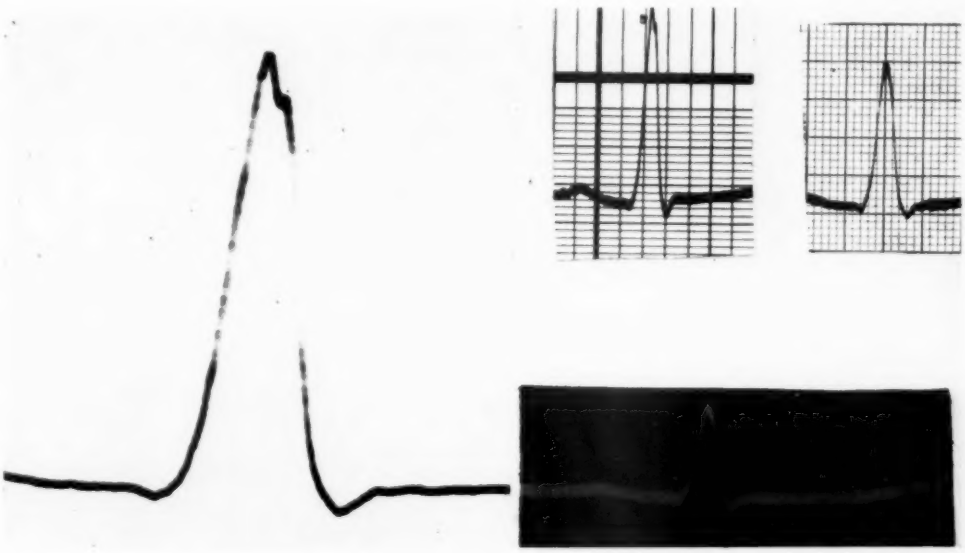


Fig. 2.—Lead II, the extremity lead of largest amplitude in a normal individual. There is a distinct notch near the peak of the R wave which is clearly seen in the cathode ray oscillograph and mirror galvanometer but not recorded by the direct writer or the string galvanometer.

Figures 2, 3, and 4 show comparative records made on the four different instruments. In Fig. 2 the notch near the peak of the deflection is clearly seen in both the C.R.O. and mirror galvanometer records. There is not a vestige of this in either the string galvanometer or direct writer records. The same is true of high frequency components in Figs. 3 and 4. The arrows in these two figures identify components which are enlarged in Figs. 5 and 6 to permit accurate measurement of their duration.

Figure 3 shows Lead II, the extremity lead of largest amplitude in an individual with longstanding angina pectoris following myocardial infarction. Notching and beading here are greater than we have observed in the extremity lead of largest amplitude in any normal individual so far. There are distinct high

frequency components at the peak and on the upper one-half of the downstroke of the R wave. These are clearly seen in the C.R.O. record and are present but not as readily visible in the record of the mirror galvanometer. They are absent in the records made by the direct writer and the string galvanometer. The arrow points to a component of the deflection that is reproduced and enlarged ten times in Fig. 5.

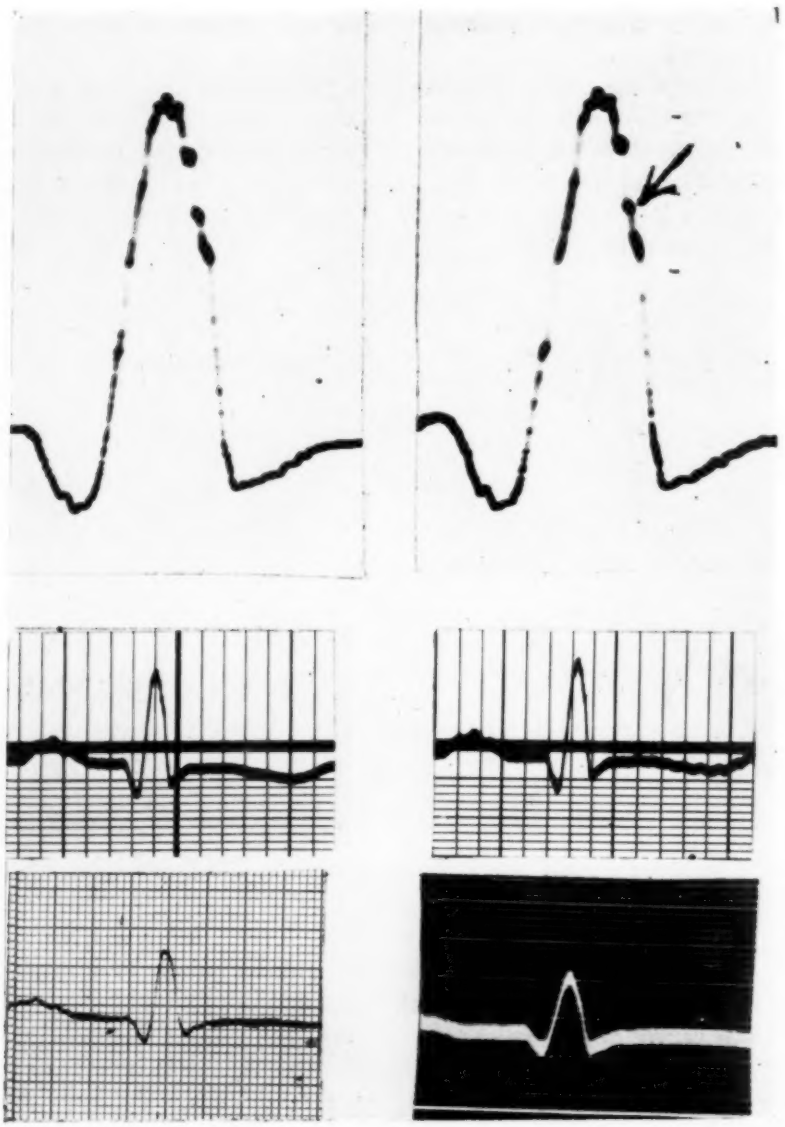


Fig. 3.—Shows very distinct notching and beading in the cathode ray oscillograph record, less distinct but still present in mirror galvanometer record, and absent in records made with the string galvanometer and the direct writer. Arrow points to notch which is enlarged ten times in Fig. 5. Two QRS complexes each of the cathode ray oscillograph records and mirror galvanometer records are mounted to show the high frequency components are consistently present.

Figure 4 is Lead V_3 from a normal individual. This transitional type deflection is frequently irregular or notched normally. On the downstroke between the peak of the R and the nadir of the S there are several high frequency components seen in the C.R.O. record. The more definite of these are also visible in the mirror galvanometer records but are absent in the records made by the direct writer and the string galvanometer. The arrow points to a component of the deflection which is enlarged in Fig. 6.

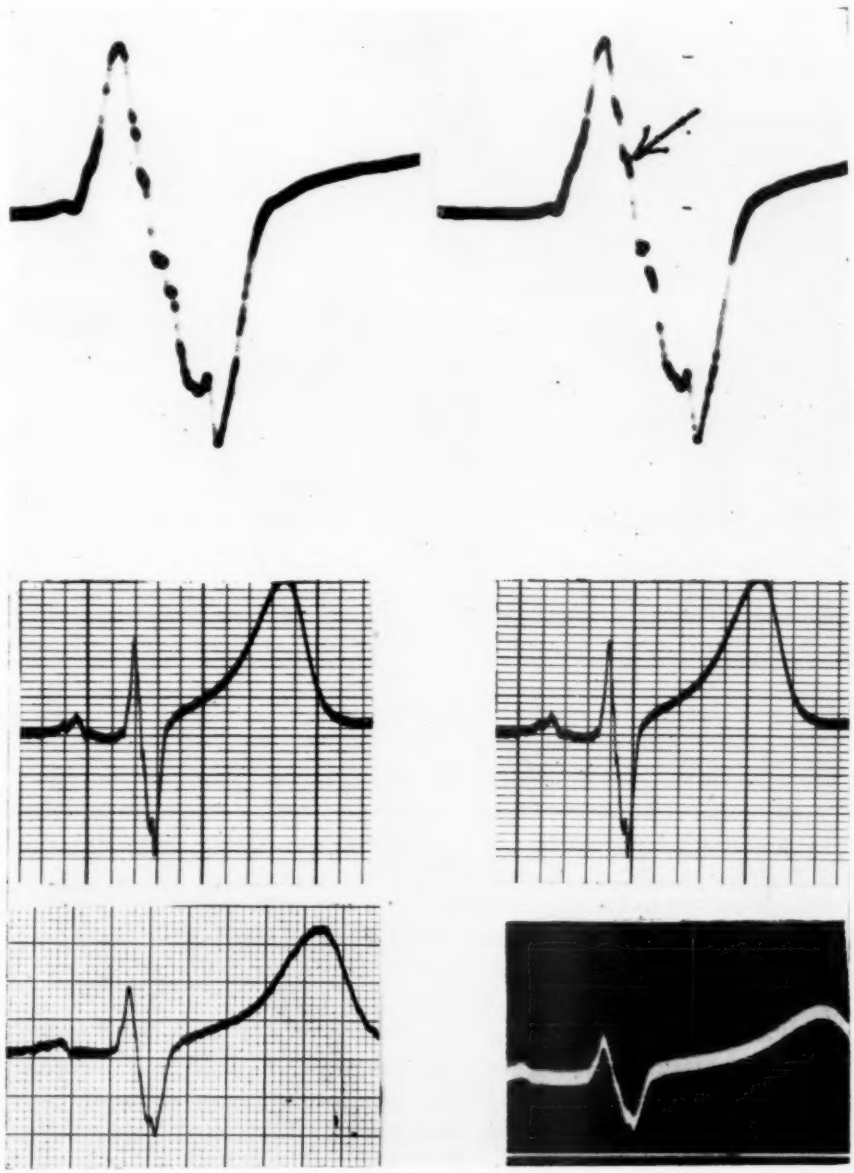


Fig. 4.—Shows very distinct notching and beading in the cathode ray oscillograph record, less distinct but still present in mirror galvanometer record, and absent in records made with the string galvanometer and the direct writer. Arrow points to notch which is enlarged ten times in Fig. 6. Two QRS complexes each of the cathode ray oscillograph records and mirror galvanometer records are mounted to show the high frequency components are consistently present.

Figures 5 and 6 are enlargements of a small part of Figs. 3 and 4, respectively. The duration of the dense component is obtained by measuring the horizontal distance it moves. If this distance and the speed with which the film moved are known, the duration of this phenomenon is determined and is found to be approximately 1/500 of a second. An instrument to reproduce this notch, even crudely, should have a deflection time which is short compared to the duration of the notch. In this case the deflection time would have to be at least as short as 1/1000 second. In terms of the shape of a frequency response curve, this requirement would correspond to a curve which was flat for several hundred cycles and which maintained at least 50 per cent response at 500 cycles.

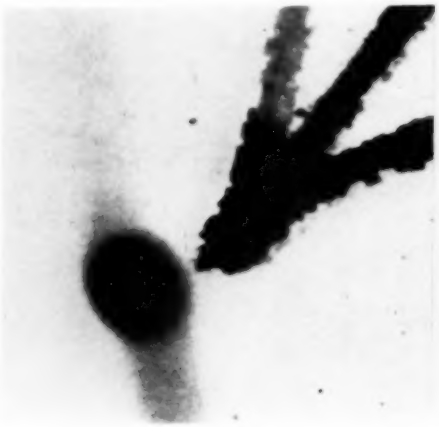


Fig. 5.

Fig. 6.

Fig. 5.—Portion of complex to which arrow points in Fig. 3 enlarged ten times. See text for explanation. Reduced one-fourth for journal reproduction.

Fig. 6.—Portion of complex to which arrow points in Fig. 4 enlarged ten times. See text for explanation. Reduced one-fourth for journal reproduction.

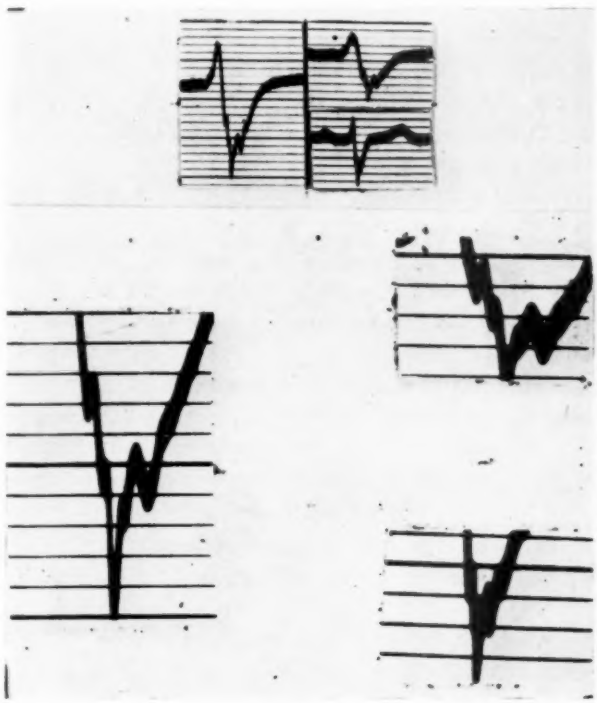
In Fig. 2 the notch observed near the peak of the R wave has been present in this individual without change in four tracings made over the past twenty months. The details selected for study as illustrated in Figs. 3 and 4 have been observed over a period of twenty and fourteen months, respectively. In all sixteen leads studied the high frequency components selected for study had been present with no significant change during the entire period of observation which ranged from twelve to twenty months. This indicates that these phenomena are not only present in repeated tracings taken on the same day but can be identified in the tracings taken months apart.

The high frequency components were best seen on the mirror galvanometer records when they occurred on a fast moving ascent or descent of the QRS. When they occurred in peaks or nadirs they were obscured to a variable degree because the slow paper speed of 75 mm. per second crowded the trace together and did not resolve the small rapid deflections. When the mirror galvanometer is run at the conventional speed of 25 mm. per second and a standardization of 1 mv. = 1 cm., a great deal more of the high frequency detail is lost. This is illustrated in Fig. 7. Therefore, the fast paper speed and adequate amplification of the signal are essential to take advantage of the high frequency response of the galvanometer.

SUMMARY AND CONCLUSIONS

1. For the high fidelity reproduction of the human electrocardiogram three properties are required of the recording instrument that are lacking in most instruments now used in routine electrocardiography. These properties are (1) high frequency response so that phenomena of 500 cycles per second or more can be reproduced; (2) adequate amplification of the signal so that a standardization of at least 1 mv. = 2 cm. can be obtained; and (3) a paper speed of at least 100 mm. per second and preferably higher.

A.



B.

Fig. 7.—Shows the same lead taken on the mirror galvanometer with three different combinations of speed and amplitude. Fig. 7, *A* shows the deflections in their original size. Fig. 7, *B* shows the nadir of each deflection enlarged four times. The one on the left was taken with a film speed of 75 mm. per second and standardization of 1 mv. = 2 cms. There are two distinct high frequency notches present. In the upper right of the field the film speed is still 75 mm. per second but the amplitude has been reduced to 1 mv. = 1 cm. These two high frequency deflections are still visible but one is almost lost. In the lower right the speed is 25 mm. per second and the standardization is 1 mv. = 1 cm. In this record neither of the previously mentioned notches can be detected.

2. With the cathode ray oscillograph and a paper speed of 350 mm. per second used as a criterion, the performance of three other electrocardiographs was tested. A string galvanometer and a direct writer were both totally inadequate for the recording of high frequency components in the electrocardiogram. However, since the clinical significance of these high frequency components is still undetermined we believe these two conventional instruments are adequate for routine clinical electrocardiography at present. A new high frequency mirror

galvanometer tested was considered to be adequate for the study of most if not all the high frequency components of the electrocardiogram.

3. An instrument employing the cathode ray oscillograph has the advantage that it can be used not only for the high fidelity electrocardiographic study of the routine standard and precordial leads, but by the addition of a second amplifier the same instrument may be used to record vectorcardiograms.

4. Certain consistently reproducible high frequency components have been present in electrocardiograms of the same individual over our maximum period of observation which at present is twenty months.

We wish to acknowledge the valuable technical assistance of Harry L. Fies.

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PHYSIOLOGIC STUDIES IN MITRAL STENOSIS

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FOR MANY YEARS it has been an accepted fact that the clinical symptoms of mitral stenosis are determined by the mechanical narrowing of the diseased valve. However, until recently surprisingly few studies had been carried out to determine the nature of the functional changes responsible for these clinical symptoms. Noteworthy exceptions to this are the early work of Lundsgaard[1] who in 1918 drew attention to the wide arteriovenous oxygen difference seen in these cases and that of Meakins and associates, who were the first to demonstrate a low cardiac output in this condition.[2] Some years later physiologic studies were also carried out by Stewart and associates[4] and by Kerkhof.[3]

Various attempts were also made by different workers to reproduce the situation, as seen in man, in experimental animals, but without much success as regards the production of chronic changes. Acute mitral stenosis in animals was studied by Katz and Spiegel.[5]

Recently there has been a renewed interest in this problem, mainly as a result of the progress made in the last few years in the surgical treatment of mitral stenosis, which although conceived at the turn of the century by Sir Lauder Brunton[6] did not become an accepted therapeutic measure until four or five years ago.[7-9]

The advent of cardiac catheterization and its accessory techniques have proved to be of great value in revealing the abnormal hemodynamical patterns characteristic of mitral stenosis.[10-13] The introduction of a method for measuring with fair approximation the pressure in the left atrium and pulmonary veins has been established by means of the pulmonary "capillary" pressure.[14] With this it is possible to determine, at least theoretically, the extent of pulmonary vascular changes in cases of mitral stenosis and to differentiate the effects of these changes on the dynamics of blood flow through the lungs from those considered to be directly attributable to the narrowing of the val e itself. The circulatory dynamics in mitral stenosis have been studied by these means by various authors.[15-19]

It is the purpose of the present report to present data on the pulmonary pressures and blood flow of nineteen patients with mitral stenosis, with particular reference to the value of these functional studies in the selection of cases for surgical treatment.

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MATERIAL AND METHODS

The patient material consisted of a total of nineteen patients with mitral stenosis of varying clinical severity. There were twelve women and seven men. The majority of these subjects had apical systolic murmurs in addition to diastolic murmurs, but none of these cases had mitral regurgitation of clinical significance, as evidenced by the lack of electrocardiographic or radiologic signs of left ventricular enlargement. In some cases a minimal degree of other valvular involvement was present, but was also considered to be clinically of no importance with the possible exception of one, (M.F.V.). The principal clinical data pertaining to these patients are seen in Table I. All patients were considered to be compensated at the time of study; those with auricular fibrillation or flutter were fully digitalized at the time. The majority of these cases were catheterized as part of a routine study prior to mitral valvuloplasty and with two exceptions were moderately to severely limited as regards their physical activity by their valvular lesions.

All cases were studied in the morning and in the postabsorptive state. In some cases a quick-acting barbiturate was given one-half hour before the procedure. The patients were rehearsed on previous days in the maneuvers to be carried out and at the same time were instructed in the use of the mouthpiece for the collection of expired air. Cardiac catheterization was performed in the usual manner.[20] Pulmonary capillary pressure was recorded after satisfactory basal conditions were obtained, the catheter was then withdrawn to the main pulmonary artery, approximately at the level of the bifurcation. An indwelling needle was inserted in the brachial artery. When pulse and respiratory rates were again stabilized cardiac output was determined by the direct Fick principle. Expired air was collected in a Douglas bag for a period of three minutes, and midway in this time blood samples were withdrawn simultaneously from the brachial and pulmonary artery.

The patient was then made to exercise by flexing and extending the legs in a bicycling manner against the resistance offered by the reciprocal movement of the arms of an assistant at the rate of one cycle per two seconds for four or five minutes. At the beginning of the third minute expired air was collected in a Douglas bag for two minutes, and midway during this period pulmonary and brachial arterial blood samples were obtained. At the end of the fourth minute pulmonary arterial pressure was recorded, after which the catheter was withdrawn to the right atrium, pressures being recorded in the right ventricle and atrium while the patient was still exercising.

The volume of expired air was measured in a Tissot spirometer and its oxygen concentration was determined by the method of Haldane and Henderson. Blood oxygen contents were determined by the Van Slyke-Neill manometric method[21] and the oxygen capacity of the blood by the tonometric method of Barcroft.[22] The arteriovenous oxygen difference was calculated as the difference between the oxygen contents of the systemic arterial blood and of the pulmonary arterial blood sample.

TABLE I. CLINICAL DATA IN PATIENTS WITH MITRAL STENOSIS

TABLE I. CLINICAL DATA IN PATIENTS WITH MITRAL STENOSIS

NUMBER	PATIENT	AGE SEX	FUNCTIONAL CLASSIFICATION	HISTORY				EXAMINATION		ROENTGENOGRAM			ELECTROCARDIOGRAM	
				EFFORT DYSPNEA		PAROXYSMAL DYSPNEA	HEMOPTYSIS	BASAL DIASTOLIC MURMUR	CONGESTIVE FAILURE	ENLARGED HEART	LEFT AURICULAR DILATATION	PULMONARY ARTERY DILATATION	RHYTHM	RIGHT VENTRICULAR HYPERTROPHY
				DURATION YEARS	SEVERITY									
1	B. C.	46 F	III	5	++	+	o	o	o	+	+	+	NSR	o
2	R. B.	24 M	III	1	++	+	o	o	o	++	+	++	NSR	++
3	A. C. L.	35 F	III	5	++	o	o	+120/80	o	++	++	++	AF	o
4	A. A.	26 M	I	0	o	o	o	o	o	o	o	–	NSR	o
5	M. L. Z.	38 F	III	5	++	o	o	o	o	++	++	++	NSR	++
6	E. V.	29 F	III	2	++	o	+	o	o	+	++	++	NSR	o
7	F. Z. F.	41 F	II	6	+	++	o	+150/90	o	+	+	+	NSR	o
8	R. P.	27 M	II	4	++	+	o	+130/90	o	+	+	+	NSR	o
9	M. F. V.	40 M	III	5	++	++	o	+130/80	o	++	++	++	AF	+
10	M. G. F.	25 F	III	2	++	+	o	o	o	++	+	++	NSR	o
11	R. V.	36 F	I	0	o	o	o	o	o	o	o	o	NSR	o
12	I. F.	41 M	III	5	++	++	o	o	o	++	++	++	AF	++
13	E. D. L.	31 F	III	2	++	++	o	o	o	++	+	++	AF	o
14	H. M. C.	30 F	II	3	+	o	o	o	o	+	+	++	NSR	o
15	E. J. V.	39 M	IV	2	++	o	o	o	o	++	+	++	AF	++
16	C. G. S.	50 F	III	6	++	o	o	o	o	++	++	++	AF	o
17	E. S. L.	27 F	II	11	++	+	++	+130/80	o	++	+	++	NSR	+
18	A. S. L.	37 F	III	5	++	o	o	o	++	++	+	++	AF	++
19	E. P.	22 M	II	2	+	o	o	+130/80	o	+	++	+	AF	+

Pressures were measured with a Sanborn Electromanometer and recorded with a direct-writing oscillograph. Mean pressures were measured by electronic integration. The zero reference point was 10 cm. anterior to the dorsal plane of the body with the patient recumbent.

Pulmonary resistances were calculated according to the following formulas:[23]

$$R_A = \frac{(PA_m - PC_m) \times 1.332 \times 60}{CO}$$

Total pulmonary resistance was calculated similarly:

$$R_T = \frac{PA_m \times 1.332 \times 60}{CO}$$

Work of the right ventricle against pressure was calculated as follows:

$$W_{RV} = \frac{CO \times PA_m \times 13.6}{1000}$$

The equivalents of the symbols used in the above formulas are as follows:

R_A = pulmonary arteriolar resistance in dynes/sec./cm.$^{-5}$
R_T = total pulmonary resistance in dynes/sec./cm.$^{-5}$
PA_m = pulmonary arterial mean pressure in mm. Hg
PC_m = pulmonary capillary mean pressure in mm. Hg
CO = cardiac output in L./min.
W_{RV} = right ventricular work against pressure in kg. M/min.

The normal values for these functions were taken from a series of normal subjects studied in Dexter's laboratory by means of the same techniques.[15,16]

RESULTS

The physiologic data corresponding to these patients are shown in Table II. The circulatory dynamics at rest are plotted in Figs. 1 and 2. In these and succeeding figures the double circles represent a particular clinical type to which reference is made later.

Oxygen consumption at rest was within high normal limits in about one-half of these patients, while slightly exceeding the normal range in the other one-half. As was to be expected it rose in all cases during exercise, this rise being roughly double the resting value in the majority of patients.

The arteriovenous oxygen difference was considerably elevated above normal in the majority of cases, with an average of 52 c.c./L. as compared with a normal average of 35. In three instances it was exceedingly high, a reflection of the increased tissue extraction of oxygen from the blood occasioned by the inadequate peripheral blood flow. This was particularly so during exercise (Fig. 3).

Cardiac Output.—The average resting cardiac output was found to be within low normal limits with a range from 1.97 to 4.76 L./Min./M.^{2} In seven cases it was below normal. The response of cardiac output to exercise was limited (Fig. 4), only four patients showing a normal increase of approximately 1 L. or more

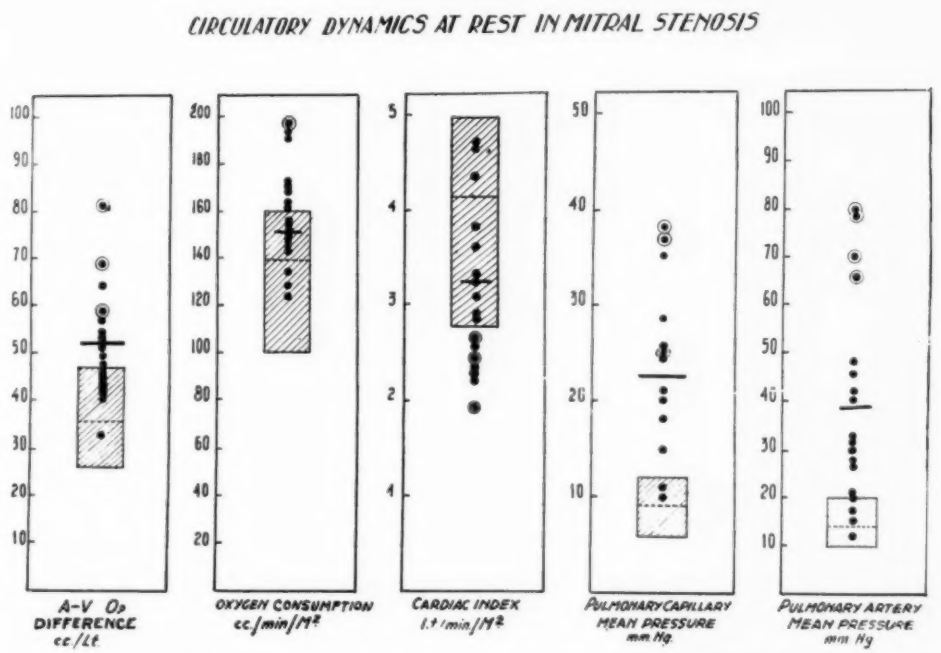

Fig. 1.—The values obtained in each case are plotted as black circles, with the horizontal line the average value for the whole group. The shaded areas represent the normal variation with the dotted line as the average normal value.

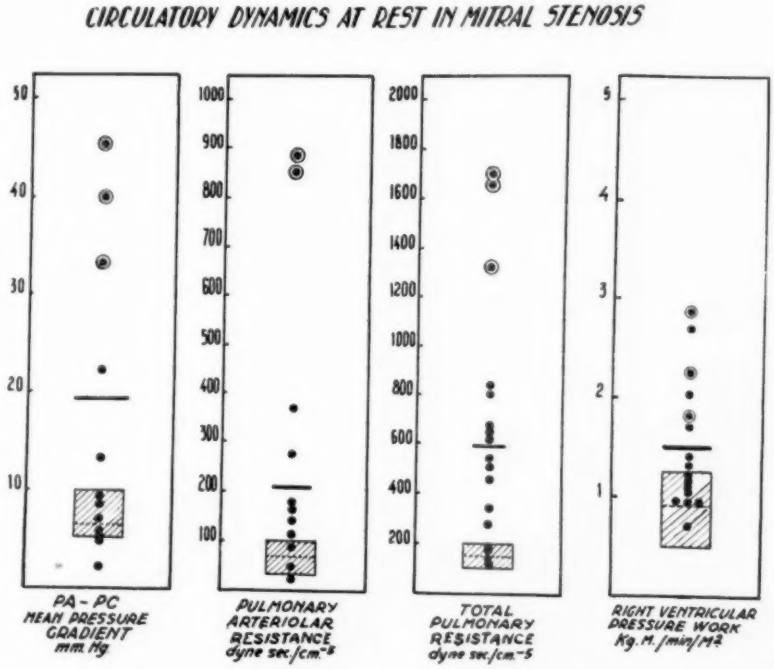

Fig. 2.—The values obtained in each case are plotted as black circles, with the horizontal line the average value for the whole group. The shaded areas represent the normal variation, with the dotted line as the average normal value.

Table II. Physiologic Data in Patients With Mitral Stenosis

NUMBER	PATIENT	AGE SEX	BODY SURFACE AREA (M^2)	CARDIAC RHYTHM	ARTERIAL OXYGEN SATURATION %		OXYGEN CONSUMPTION (c.c./min./M^2)		A. V. OXYGEN DIFFERENCE (c.c./L.)		CARDIAC INDEX (L./min./M^2)	
					REST	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST	EXERCISE
1	B. C.	46 F	1.43	NS	92.8		169		44.3		3.82	—
2	R. B.	24 M	1.68	NS	96.6		142		48.1		2.94	—
3	A. C. L.	35 F	1.65	AF	94.4	94.5	122	222	52.5	96.9	2.32	2.29
4	A. A.	26 M	1.66	NS	95.0	98.0	199	556	41.8	76.7	4.76	7.25
*5	M. L. Z.	38 F	1.40	NS	91.0	94.0	155	345	58.2	118.0	2.67	3.09
6	E. V.	29 F	1.61	NS	84.3	—	144	348	46.6	84.9	3.09	3.75
7	F. Z. F.	41 F	1.53	NS	94.4	—	144	—	54.1	—	2.66	—
8	R. P.	27 M	1.81	NS	91.1	93.0	161	388	45.0	83.3	3.59	4.65
9	M. F. V.	40 M	1.77	A. Flutter	95.0	98.0	144	250	64.1	104.8	2.25	2.39
10	M. G. F.	25 F	1.47	NS	91.6	92.0	145	—	43.0	—	3.36	—
11	R. V.	36 F	1.72	NS	97.8	—	185	302	42.5	53.9	4.35	5.61
*12	I. F.	41 M	1.68	AF	91.0	97.0	168	286	69.7	112.0	2.41	2.58
13	E. D. L.	31 F	1.59	AF	97.0	—	128	210	45.9	88.2	2.78	2.38
14	H. M. C.	30 F	1.56		94.0	—	148	217	32.2	48.8	4.64	4.83
*15	E. J. V.	39 M	1.58		92.5	—	161	—	82.0	—	1.97	—
16	C. G. S.	50 F	1.54	AF	94.5	97.0	136	288	51.4	72.7	2.65	3.96
17	E. S. L.	27 F	1.50	NS	92.6	96.0	145	318	56.9	95.0	2.54	3.35
*18	A. S. L.	37 F	1.44		—	—	194	264	—	—	—	—
19	E. P.	22 M	2.06	AF	95.4	98.0	170	283	52.7	82.8	3.23	3.42
Average		32	1.61		94.0	96.0	156	304	51.8	83.6	3.11	3.82

*These patients are represented in the graphs by the following symbol: ⊙

TABLE II PHYSIOLOGIC DATA IN PATIENTS WITH MITRAL STENOSIS (CONTINUED)

NUMBER	PATIENT	AGE SEX	PULMONARY ARTERIAL PRESSURE (mm.Hg)				PULMONARY CAPILLARY MEAN PRESSURE (mm.Hg)		RIGHT VENTRICULAR DIASTOLIC PRESSURE (mm.Hg)		RIGHT ATRIAL MEAN PRESSURE		PULMONARY ARTERIOLAR RESISTANCE (dyne/sec./cm.^{5})	TOTAL PULMONARY RESISTANCE (dyne/sec.cm.^{5})		RIGHT VENTRICULAR WORK (kg.M/min./m.)^2	
			REST		EXERCISE		REST	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST	REST	EXERCISE	REST	EXERCISE
			S/D	M	S/D	M											
1	B. C.	46 F	30/20	10	—	—			0	—	5	—	—	293	—	1.04	—
2	R. B.	24 M	28/10	17	—	—	20		8	—	—	—	—	—	—		—
3	A. C. L.	35 F	39/22	30	52/24	39	25		—	—		—	10.4	626	—	0.95	—
4	A. A.	26 M	19/7	15	31/15	20	10		—	—	—	—	51.4	152	145	0.97	1.97
*5	M. L. Z.	38 F	103/53	78	115/75	92	—		—	—	6	—	—	1670	1970	2.84	4.00
6	E. V.	29 F	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7	F. Z. F.	41 F	35/15	26	48/24	36	18		5		—	—	15.7	510	—	94	—
8	R. P.	27 M	36/15	27	62/25	50	20	52	—	0	—	—	363| 304	333	475	1.32	3.16
9	M. F. V.	40 M	42/18	30	70/45	55			15	—	12	—	—	602	1040	0.92	1.79
10	M. G. F.	25 F	34/10	22	—	—	15					—	106	332	—	1.08	—
11	R. V.	36 F	23/6	12	28/7	14	11	—		2	—	—	21.4	128	116	0.71	1.07
*12	I. F.	41 M	100/50	70	125/75	100	25	—		25	—	—	890	1380	1850	2.30	3.51
13	E. D. L.	31 F	58/35	45	95/37	55				2	—	6	—	812	1160	1.71	1.79
14	H. M. C.	30 F	49/26	42	58/28	44	29	36		15		12	143| 7.92	464	466	2.72	2.90
*15	E. J. V.	39 M	82/58	65	97/70	85	35	—					848	1750	—	1.82	—
16	C. G S.	50 F	48/26	32	77/55	62		—	12		12	25	—	626	813	1.16	3.34
17	E. S. L.	27 F	59/25	40	77/35	64	32	—		15	—	15	168	840	1010	1.38	2.92
*18	A. S. L.	37 F	105/65	78	130/75	95	38	—		—	—	—	—	—	—	—	—
19	E. P.	22 M	60/36	18	80/49	61	26	—		26	—	—	265	578	798	2.09	2.97
Average		32	52/28	39	76/43	58	22	—	8	11	9	14	274	694	890	1.50	2.67

per M^2 and in one of these (R.P.) the response can be considered abnormal, as the arteriovenous oxygen difference during exercise exceeded 60 c.c./L. In the remaining ten studies in which exercise was carried out there was no significant increase, in spite of the fact that the oxygen consumption was appreciably augmented in all. It can be seen that the two subjects whose functional classification corresponded to Group I showed a normal increase in cardiac output. In one of these patients (A.A.) the resting oxygen consumption was more than trebled with exercise.

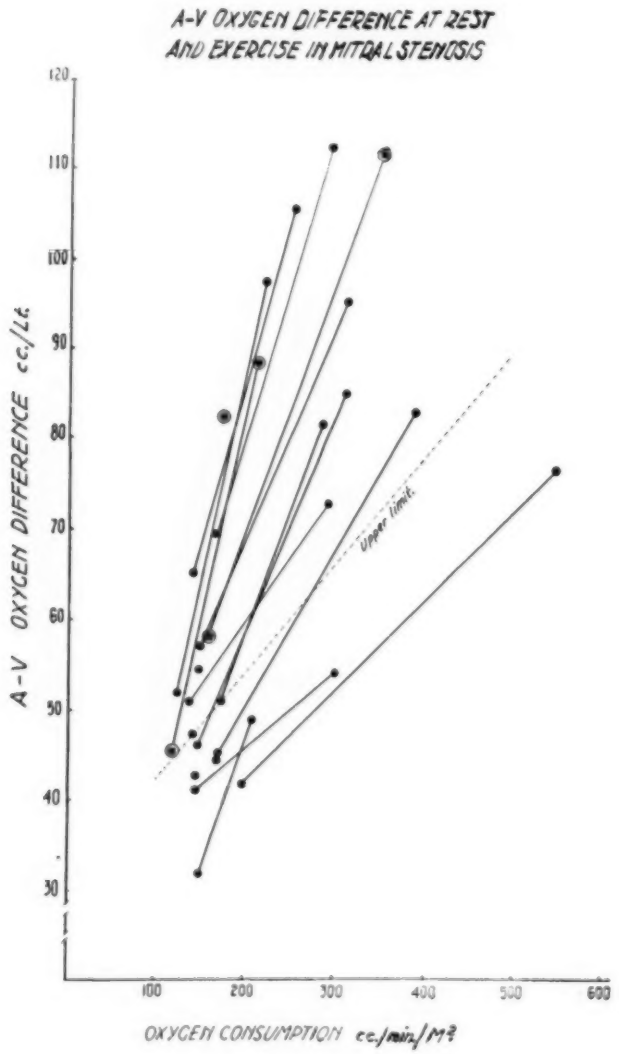

Fig. 3.—Each pair of black circles joined by the corresponding lines represents the atrioventricular oxygen difference for each case at rest and exercise plotted against the oxygen consumption. The upper limit is marked by the dotted line.

Pulmonary Capillary Pressure.—The mean pulmonary capillary pressure was elevated in all patients with the exception of the same two whose functional behavior was within normal limits in all studies. The average for the group was 22 mm. Hg, ranging from 10 to 38 mm. Two of the three cases showing extreme values corresponded to the patients identified by the double circles.

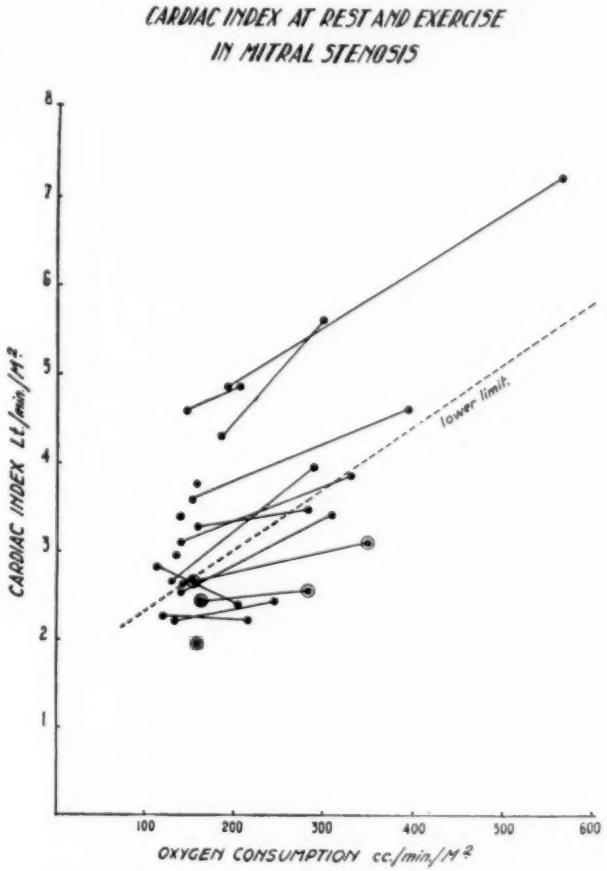

Fig. 4.—Each pair of black circles joined by the corresponding lines represents the values obtained for the cardiac index, at rest and exercise, plotted against the oxygen consumption. The dotted line marks the lower limit of normal.

Pulmonary Arterial Pressure.—Pulmonary artery mean pressure averaged slightly more than three times normal at rest, ranging from normal values (four cases) to extremes of 78 mm. Hg. During exercise the pulmonary arterial pressure was considerably increased in all save the two patients belonging to Group I previously referred to (Fig. 5). The patients represented by the double circles were the ones that had the highest values, both at rest and exercise.

PA–PC Pressure Gradient.—In seven cases the elevation of pulmonary arterial pressure was related to the increased capillary pressure, and in the remaining four in which both these pressures were obtained the pulmonary arterial pressure was elevated out of proportion to the capillary pressure. Three of these four patients showed the PA–PC mean pressure gradient to be markedly increased.

The *average pulmonary arteriolar resistance* was roughly double the normal value. However the individual results varied within wide extremes, with the majority fairly close to the normal range. In two cases, marked by the double circle, this resistance was very high.

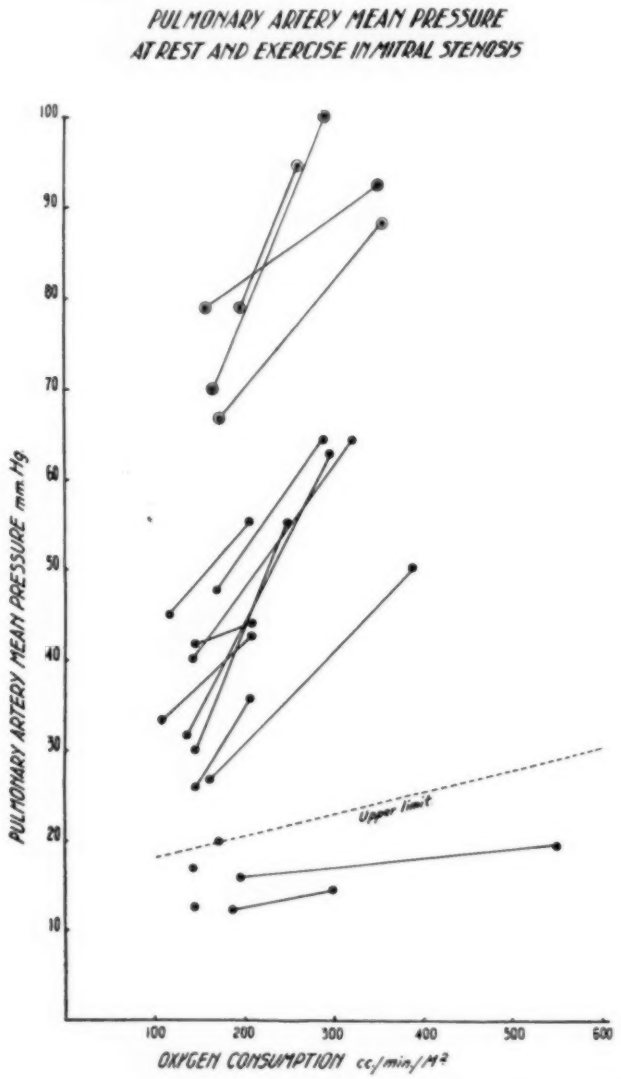

Fig. 5.—Each pair of black circles joined by the corresponding lines represents the pulmonary arterial mean pressure of each case, at rest and exercise, plotted against the oxygen consumption. The dotted lines represent the normal limits.

The *total pulmonary resistance* also varied within wide limits, with an average resting value of nearly three times the normal. Here again the cases showing the most extreme variation from normal corresponded to the patients with the most severe clinical picture. During exercise this resistance was seen to increase in all except those cases in which it was normal at rest (Fig. 6).

The *right ventricular work against pressure* was above the normal in all subjects with one exception. The average values were twice normal at rest and three times normal during exercise (Fig. 7).

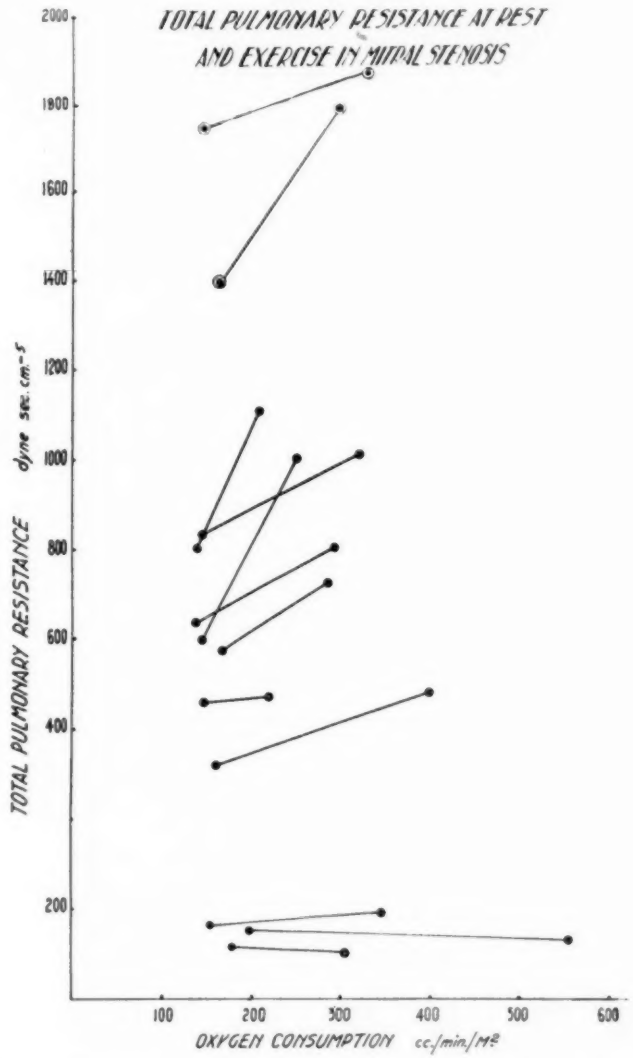

Fig. 6.—The changes in total pulmonary resistance are seen plotted against the oxygen consumption at rest and during exercise.

DISCUSSION

Narrowing or stenosis of the mitral valve constitutes an impediment to the flow of blood from the left auricle into the left ventricle. As the rate of flow through this valve depends upon the pressure gradient across the valve, it follows that an increase in left atrial and pulmonary vascular pressures is necessary to maintain an adequate left ventricular inflow.

The pressure changes seen in our cases are in accordance with the observations of other workers who have previously studied this problem. Of special importance is the relationship between the elevation of the pulmonary arterial and pulmonary capillary pressure, which, when altered as a result of a disproportionate increase of the pulmonary arterial pressure, reflects the presence of an increased resistance at the level of the pulmonary arteriolar bed. If we accept that the pulmonary capillary pressure is a faithful measure of the pulmonary venous pressure and that of the left atrium, it is possible to determine the extent of these pulmonary vascular changes in mitral stenosis and to differentiate between the effects of such changes and the effects attributable to the narrowing of the valve itself on the dynamics of blood flow through the lungs, a differentiation of considerable importance at this time because of the recent interest in operative attacks on the stenosed mitral valve.

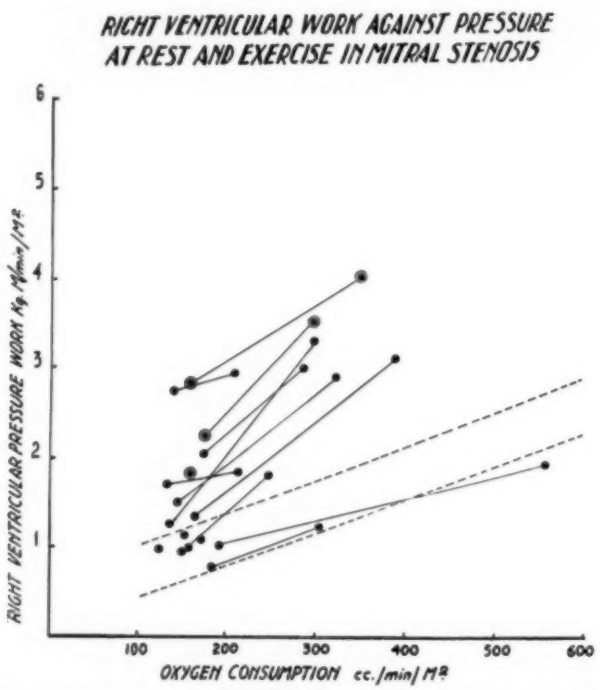

Fig. 7.—The variation in the work of the right ventricle is shown, at rest and during exercise, in terms of oxygen consumption. The dotted lines serve as an approximate zone of reference, representing the limits of variation seen in normal subjects.

The pathogenesis of these vascular changes is not clearly understood. Pathologic studies have revealed organic changes in the arterioles of the lungs of patients with mitral stenosis such that the lumina of these vessels were markedly decreased in size.[24-26] However, there appears to be indirect evidence that points to the fact that this decrease in the cross sectional area of the pulmonary arteriolar bed can also be due to arteriolar constriction. The existence of these functional reversible factors would appear to be substantiated by the considerable reduction in pulmonary arteriolar resistance reported in quite a few cases after

surgical widening of the diseased mitral valve. Further support of the presence of these physiologic factors, in some cases at least, is the fact that the pulmonary arteriolar resistance has been seen to remain stationary or actually decrease during exercise.

A definite inverse correlation was found between resting cardiac output and total pulmonary resistance in cases of tight mitral stenosis (Fig. 8) in keeping with the results obtained by other workers.[18,19] Similarly, a correlation between the cardiac output and the pulmonary arterial pressure shows that flow tends to decrease as pressure rises (Fig. 9).

It is an established fact that cardiac output does not increase in cases of tight mitral stenosis during exercise, despite the increase in oxygen consumption. This is to be seen in ten of our cases.

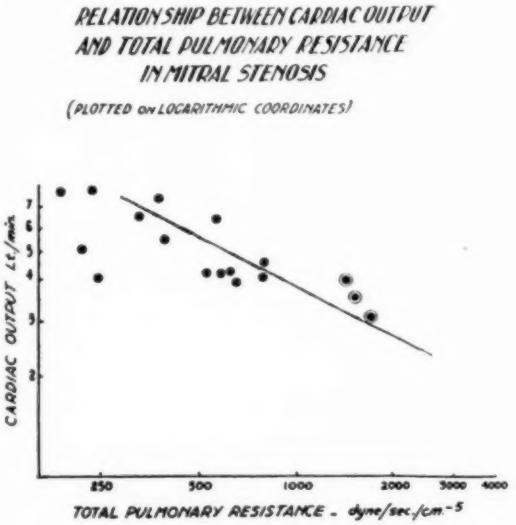

Fig. 8.

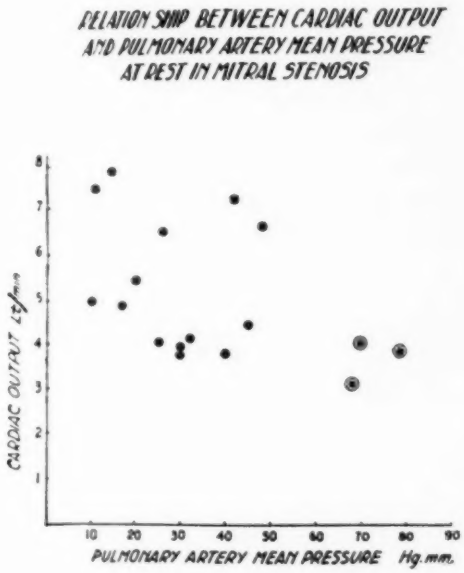

Fig. 9.

Fig. 8.—Cardiac output and total pulmonary resistance are plotted on logarithmic coordinates. Note the straight line relationship between these two functions.

Fig. 9.—Cardiac output and pulmonary arterial mean pressure are plotted on ordinary coordinates.

It is difficult to explain why the cardiac output does not show a proportionate increase during exercise, with no apparent breaking of the equilibrium between the output of both ventricles, which would determine acute edema of the lungs in some cases, which show no evidence of right ventricular incompetence or of tricuspid insufficiency. It is our surmise that in this situation the following events occur. During exercise there is a small, initial rise in right ventricular output, which in the presence of an increased resistance and high pulmonary arterial pressure, produces a state of pulmonary engorgement or congestion; this in turn acts reflexively on the pulmonary arteriolar bed, giving rise to vasoconstriction which determines a further elevation of pulmonary arterial pressure. It has been argued that the arteriolar resistance serves to protect the capillaries in this respect.[18] However, this increased resistance would appear to constitute a real handicap to the right ventricle, leading to its rapid enlargement. Under

these circumstances and on account of the marked increase in the pulmonary arteriolar resistance, the patients follow a course that in all respects is similar to that of cor pulmonale.

The pressure in the pulmonary artery rises progressively at the beginning of exercise and is then maintained. The blood that accumulates initially in the lungs breaks the equilibrium between the two ventricles, but this is quickly regained as a result of a reduction of the output of the left ventricle, with concomitant peripheral vasoconstriction so as to maintain systemic blood pressure. In this way the amount of blood returned to the right ventricle is reduced.

In this series of patients, four are of particular interest, represented in the graphs by double circles, inasmuch as their clinical and functional behavior characterize them as a group apart. These patients have been labeled by one of us (ACT) "mitral stenosis with cor pulmonale."[27] Another characteristic of these patients is their rapidly downhill clinical course, with early congestive failure.

From a functional point of view the behavior of these patients also shows a definite pattern, characterized chiefly by extremely high pressures in the pulmonary circuit with low, fixed cardiac outputs. The four cases which figure in the present series (M.L.Z., I.F., E.J.V. and A.S.L.) had by far the highest pressures of the whole group. In fact, three of these four patients had resting pulmonary arterial pressures in the range of normal systemic blood pressure. During exercise extreme elevations were registered in all four. The pulmonary capillary pressure was also markedly elevated, approaching 40 mm. in two patients. However, the pulmonary arterial pressure was increased out of proportion to the capillary pressure, giving rise to a great increase in pulmonary arteriolar resistance.

The total pulmonary resistance was also greatly increased in the three cases in which it could be determined. As a consequence of these findings the right ventricle was forced to suffer marked increase in its work against pressure. In one of these patients (I.F.) the diastolic filling pressure of the right ventricle as evidenced by the mean right atrium pressure in the absence of signs of tricuspid valve lesions, which were eliminated by analysis of the pressure tracings, was markedly increased, thus showing that the right ventricle, already overtaxed at rest was unable to meet the demands placed on it during exercise.

SUMMARY

Physiologic studies were carried out in a series of nineteen patients with predominant mitral stenosis, at rest and during exercise, by means of cardiac catheterization and its accessory techniques.

The pressures in the pulmonary circuit and blood flow of these patients, already altered at rest, were further increased during exercise.

The pulmonary vascular changes present in some of these cases are analyzed and their pathogenesis discussed. The clinical and physiologic behavior of patients in which these vascular changes are pronounced are shown to be easily differentiated from those cases with minimal involvement.

The implications of marked changes in the pulmonary vasculature are discussed from the point of view of valvular surgery.

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THE CHARACTERISTICS OF THE RIGHT ATRIAL PRESSURE WAVE ASSOCIATED WITH RIGHT VENTRICULAR HYPERTROPHY

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THE *a* wave of the venous pulse tracing, which is the graphic representation of contraction of the right atrium, has been a subject of interest to the clinician and physiologist for many years. Mackenzie[1] demonstrated prominence of the *a* wave in patients with tricuspid stenosis by the use of the venous polygraph. The association of a prominent presystolic venous wave with tricuspid stenosis has persisted to the present and little attention has been directed to the occurrence of this wave with other cardiac lesions.

However, in 1913, Laubry and Pezzi[2] described high *a* waves in the venous polygraphs of five patients with congenital heart disease. Recently, Grishman and associates[3] have demonstrated the presence of presystolic hepatic pulsations associated with several forms of cardiac disease. With the introduction of cardiac catheterization a more precise evaluation of the right atrial pressure characteristics in human subjects has been possible. Abrahams and Wood[4] have presented right atrial pressure tracings from patients with isolated valvular pulmonic stenosis showing *a* waves of increased amplitude which they have termed "giant *a* waves." Maraist and associates[5] and Engle and Taussig[6] have also described high right atrial pressures in isolated valvular pulmonic stenosis. Dresdale and associates[7] reported elevated right atrial pressures in three patients with primary pulmonary hypertension and presented right atrial pressure tracings showing a high amplitude *a* wave.

In this laboratory prominent *a* waves have been observed in the right atrial pressure tracings recorded in patients with hypertrophy of the right ventricle. These right atrial pressure contours show a similar configuration regardless of the underlying disease process responsible for the hypertrophy of the right ventricle, and they are, therefore, presented as representing a characteristic response of the right atrium to right ventricular hypertrophy.

Isolated valvular pulmonic stenosis and idiopathic pulmonary hypertension are the two entities in our experience that result in the most severe grades of right ventricular hypertrophy. The right atrial pressure tracings in patients with these lesions are, therefore, presented, and the basis for the development of the large *a* waves is discussed.

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MATERIAL AND METHODS

Twenty-two patients with isolated valvular pulmonic stenosis and eight patients with idiopathic pulmonary hypertension have been studied by cardiac catheterization. Pressures were measured by means of Statham strain gauges and a Hathaway recording apparatus. The zero point of reference was 10 cm. above the patient's back in the supine position. The blood samples were analyzed for oxygen by the Van Slyke-Neill[8] manometric method.

The diagnosis of isolated valvular pulmonic stenosis was confirmed in all cases by the pressure differential between the pulmonary artery and the right ventricle. The diagnosis of idiopathic pulmonary hypertension was made on the finding of a markedly elevated pulmonary artery pressure and by the exclusion of all known disease entities capable of producing pulmonary hypertension.

RESULTS

A. *Isolated Valvular Pulmonic Stenosis.*—Of the twenty-two patients with this congenital cardiac anomaly that have been studied by cardiac catheterization, the pressure tracings from the right atrium permitted accurate measurement and timing with the simultaneous electrocardiogram in fifteen instances. In thirteen of these fifteen pressure tracings an *a* wave of increased amplitude was present. The onset of this wave occurred 0.06 to 0.10 second following the onset of the P wave of the simultaneous electrocardiogram. The maximum amplitude of these *a* waves ranged from 8 to 17 mm. Hg and in eight instances this level was greater than 12 mm. Hg. A drop in pressure in the right atrium from the summit of the *a* wave to low levels of from 1 to 5 mm. Hg occurred during ventricular systole. This was followed by a slow rise in pressure to levels varying from 4 to 10 mm. Hg at the end of ventricular systole. A decrease in pressure then occurred during early ventricular diastole terminating in the sharp rise of the *a* wave in late ventricular diastole. The early diastolic pressure in the right ventricle was within normal limits in all instances, thus indicating the competency of the right ventricle. The amplitude of the *a* wave tended to vary directly with the amplitude of the right ventricular systolic pressure. The pressure in the right ventricle during systole ranged from 47 to 221 mm. Hg in the thirteen patients with high *a* waves. In the patients with an *a* wave of 12 mm. Hg or greater the right ventricular systolic pressure was greater than 110 mm. Hg. In the two patients whose right atrial pressure tracings did not show high *a* waves the right ventricular pressure was 41 and 46 mm. Hg. The P wave in Lead II of the electrocardiogram was 2.5 mm. or greater in amplitude in six instances, with the highest P wave measuring 5 mm. in height. Prolongation of the intrinsicoid deflection time in Lead V_1 was greater than 0.03 second in eleven of these patients. Enlargement of the right atrium was observed at fluoroscopy in seven of the thirteen patients.

The right atrial pressure tracing from a thirteen-year-old girl with isolated valvular pulmonic stenosis is shown in Fig. 1. A giant *a* wave is noted occurring 0.06 second following the preceding P wave, and rising to a peak of 17 to 19 mm. Hg. The systolic pressure in the right ventricle was 187 mm. Hg, whereas the pulmonary artery systolic pressure was 21 mm. Hg.

Fig. 1.—The right atrial pressure tracing from a patient with isolated valvular pulmonic stenosis. The scale represents pressure in millimeters of mercury.

In seven of the thirteen patients with high *a* waves the catheter was advanced into the left atrium and into a pulmonary vein, presumably through a patent foramen ovale. In five of these patients there was a significant unsaturation of the peripheral arterial blood with levels of from 57 to 88 per cent saturation. Each of these five patients demonstrated a pressure gradient from the right atrium to the left atrium. In the two patients with a patent foramen ovale without peripheral arterial unsaturation no gradient was present.

Figure 2 shows the pressures recorded during the withdrawal of the catheter from the left to the right atrium in one of these seven patients. A significant

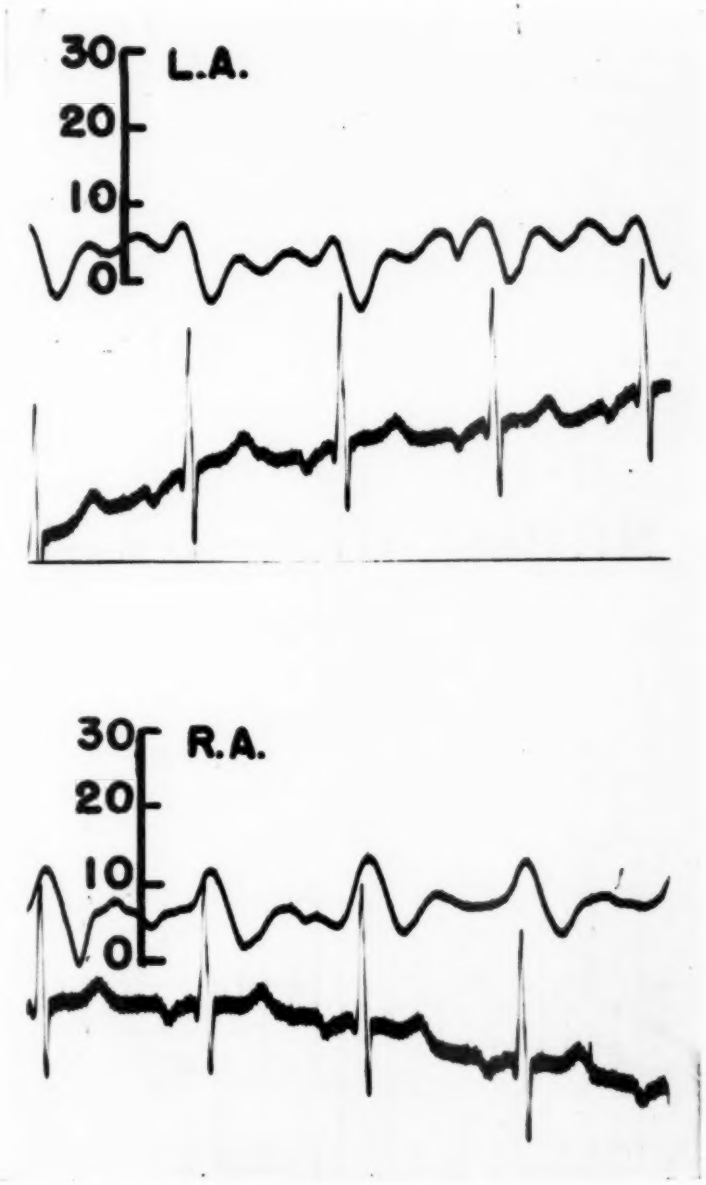

Fig. 2.—The pressure tracings recorded during the withdrawal of the catheter from the left atrium (upper tracing) to the right atrium (lower tracing) in a patient with isolated valvular pulmonic stenosis.

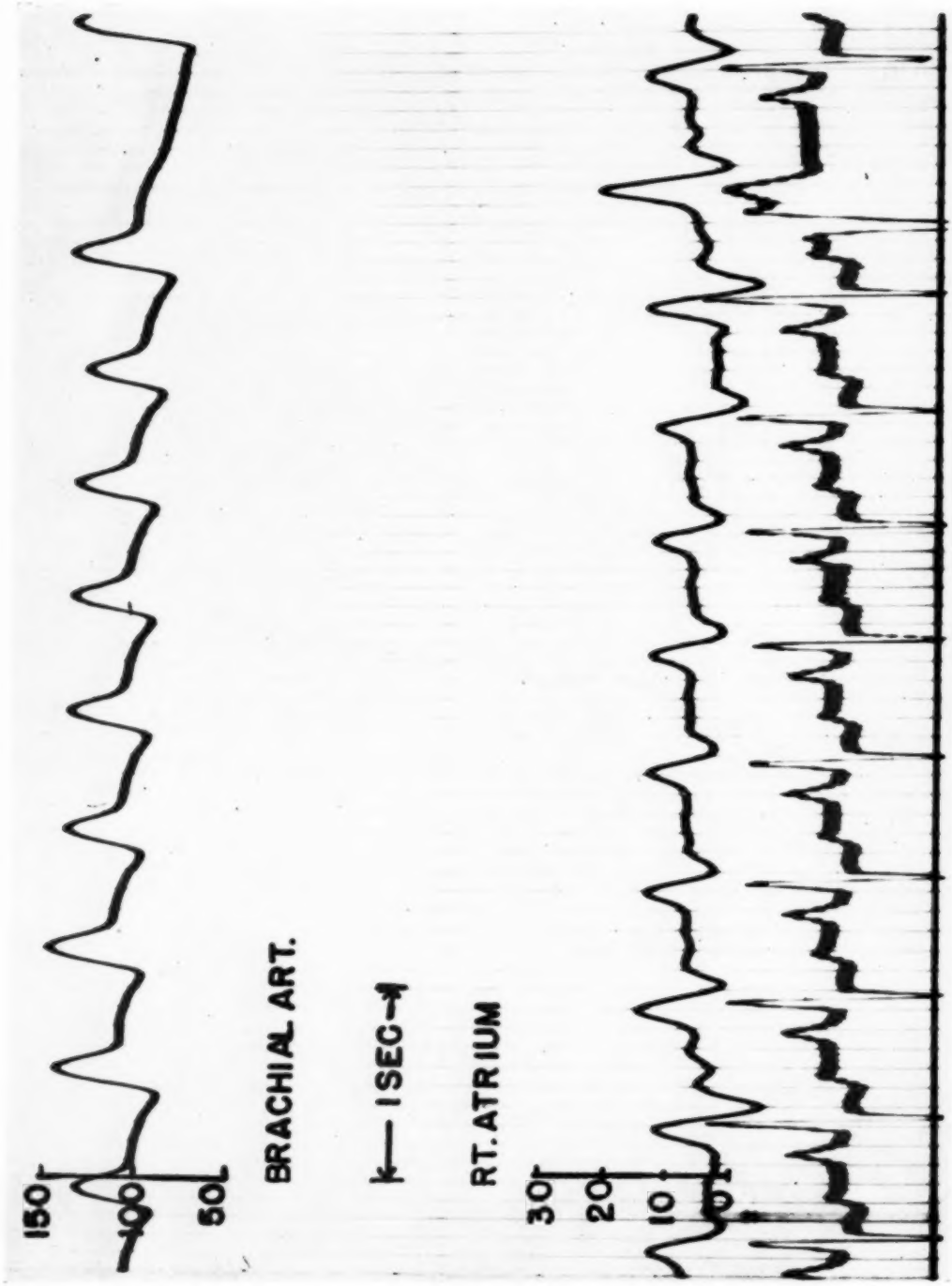

FIG. 3.—The pressure tracings from the brachial artery and right atrium in a patient with idiopathic pulmonary hypertension.

pressure gradient from the right to the left atrium is apparent. A difference in the configuration of the pressure waves in the two atria is also present with the giant *a* wave occurring in the right atrium. In this eleven-year-old boy the peripheral arterial oxygen saturation was 79 per cent, while oxygen saturation of the pulmonary venous blood was 99 per cent. The pressure in the right ventricle during systole was 144 mm. Hg and in the pulmonary artery 12 mm. Hg. There was a delayed intrinsicoid deflection time of 0.04 second in Lead V_1 of the electrocardiogram.

B. *Idiopathic Pulmonary Hypertension.*—Seven of the eight patients with a diagnosis of idiopathic pulmonary hypertension showed *a* waves of increased amplitude in the right atrial pressure tracings. These waves ranged in amplitude from 10 to 27 mm. Hg. The right ventricular systolic pressure ranged from 60 to 140 mm. Hg. In three patients the early right ventricular diastolic pressure was within normal limits while in the remaining four patients there was an elevation of the right ventricular pressure throughout diastole. The pulmonary artery pressure was elevated in all instances with a systolic pressure identical to that in the right ventricle. The intrinsicoid deflection time in Lead V_1 of the electrocardiogram was prolonged beyond 0.03 second in all seven patients and high amplitude P waves were present in three.

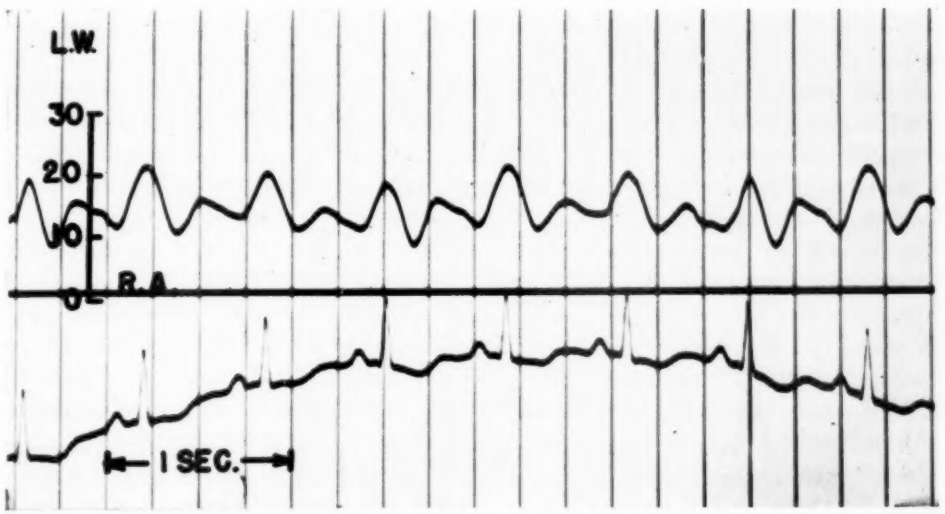

Fig. 4.—The right atrial pressure tracing from a patient with idiopathic pulmonary hypertension.

The right atrial pressure tracing in a forty-year-old woman is shown in Fig. 3. An *a* wave 13 mm. in amplitude is seen with an onset 0.08 second following the P wave of the electrocardiogram. The right ventricular pressure in this patient was 140/0/10 mm. Hg and the pulmonary artery pressure 140/70 mm. Hg at rest with a rise to 200/86 mm. Hg following exercise. The peripheral arterial oxygen saturation was 73 per cent.

The right atrial pressure tracing from a second patient in this group is shown in Fig. 4. In this tracing, however, there is an elevated pressure level throughout diastole, the early diastolic pressure being 11 mm. Hg indicating failure of the

Fig. 3.—The pressure tracings from the brachial artery and right atrium in a patient with idiopathic pulmonary hypertension.

right ventricle. Nonetheless, the giant *a* wave is still clearly evident, rising to a peak of 21 mm. Hg. The right ventricular pressure was 140/12 mm. Hg and the pulmonary artery pressure was 140/55 mm. Hg.

DISCUSSION

A. *The Origin of Giant a Waves Associated with Right Ventricular Hypertrophy.*—The mechanisms underlying the development of the increased amplitude of the *a* wave in the presence of right ventricular hypertrophy have not been well established. Laubry and Pezzi[2] expressed the opinion that the high *a* waves noted in the venous pulse tracings in patients with congenital heart disease represented a response on the part of the right atrium to an elevation of the right ventricular diastolic pressure. Engle and Taussig[6] proposed that the elevated right ventricular diastolic pressure was the principal factor resulting in the elevated right atrial pressure observed in patients with isolated valvular pulmonic stenosis. Acute experiments in animals have clearly demonstrated an elevation of right ventricular diastolic pressure in response to an increased work load imposed on the right ventricle. Thus, the studies of Fineberg and Wiggers[9] and of Brecher and Opdyke[10] utilizing progressive constriction of the pulmonary artery demonstrated a resulting rise in right ventricular diastolic and right atrial pressure. However, with severe grades of pulmonary artery constriction the right atrial pressure tracings revealed a pattern of tricuspid insufficiency and not the development of a high *a* wave.

It is proposed at this time that a more significant factor in the genesis of the giant *a* wave is the alteration of the pressure-volume relationship of the right ventricle that occurs with hypertrophy of this chamber. A consideration of the pressure relationship between the left and right atria in normal hearts and in the presence of an atrial septal defect is of importance in emphasizing this factor. Opdyke and associates[11] have shown that the left atrial pressure in dogs in the majority of instances exceeds the right atrial pressure during all phases of the cardiac cycle. It was also shown that the left atrial-venous system was less distensible than the right. It has been demonstrated by Cournand and associates[12] and by Dexter and associates[13] that in patients with atrial septal defects the left atrial pressure exceeds that in the right atrium with a resulting left-to-right blood flow and greater filling of the right ventricle than the left. This pressure relationship in the two atria in normal dogs and in patients with atrial septal defects is probably a reflection of the relative resistance to filling of the two ventricles, the thicker walled left ventricle being less distensible than the right ventricle. Thus, as postulated by Barger and associates,[14] in the presence of an atrial septal defect of such magnitude as to render the two atria a common chamber with a uniform pressure, the blood flow would still be from left to right with greater filling of the right ventricle owing to the greater distensibility of this chamber.

However, when hypertrophy of the right ventricle occurs as a result of a chronic increase in the work load, as in the two entities considered in this report, the normal degree of distensibility of the right ventricle is no longer present. With the normal low pressure in the right atrium filling of the less distensible hypertrophied right ventricle is incomplete and a residual volume of blood re-

mains in the right atrium. Hypertrophy of the right atrium occurs as a consequence and the increased force of contraction is manifest by the development of an *a* wave of increased amplitude.

In accordance with this viewpoint it is to be noted that there was no clinical evidence of right ventricular failure in the patients with isolated valvular pulmonic stenosis or in three of the patients with idiopathic pulmonary hypertension. In these patients the early diastolic pressure in the right ventricle was not elevated. In the four patients with clinical signs of right ventricular failure, the right ventricular diastolic pressure was elevated throughout diastole. However, the dominant wave of the right atrial pressure tracing was the *a* wave in all instances, and there was no graphic evidence of tricuspid insufficiency.

B. *The Significance of Giant a Waves Associated with Right Ventricular Hypertrophy.*—The peripheral manifestations of a high amplitude *a* wave may be of value in the clinical evaluation of patients with severe right ventricular hypertrophy. An excellent description of the presystolic pulsations seen in the neck veins in patients with isolated valvular pulmonic stenosis has been given by Abrahams and Wood,[4] who designated this pulsation a "venous Corrigan pulse." Grishman and associates[3] have emphasized the presystolic hepatic impulse detectable in some patients with high *a* waves.

The demonstration of a pressure gradient from the right to the left atrium in patients with isolated valvular pulmonic stenosis and a patent foramen ovale establishes the basis for the presence of cyanosis in these patients. This origin of arterial unsaturation has been discussed by Engle and Taussig[6] in their description of this disease. This mechanism may also be a major factor in producing cyanosis in patients with idiopathic pulmonary hypertension when such occurs.

The presence of high amplitude *a* waves in the right atrial pressure tracings of patients with rheumatic heart disease is of considerable interest in the light of this proposed characteristic right atrial pressure pattern resulting from right ventricular hypertrophy. High amplitude *a* waves have been observed in this laboratory in patients with mitral stenosis being evaluated for mitral commissurotomy. As it has not been possible to definitely establish the presence or absence of tricuspid valve stenosis in all these patients they have not been included in this report of high amplitude *a* waves occurring solely as a result of right ventricular hypertrophy. The fact that such waves may be a manifestation of hypertrophy of the right ventricle and not an indication of stenosis of the tricuspid valve is of vital interest since surgical correction of valvular stenosis has become an established procedure.

CONCLUSIONS

1. The right atrial pressure tracings recorded in thirteen patients with isolated valvular pulmonic stenosis and in seven patients with idiopathic pulmonary hypertension demonstrated an *a* wave of increased amplitude.

2. It is proposed that this giant *a* wave represents a characteristic response of the right atrium in the presence of severe right ventricular hypertrophy.

3. The origin and significance of this pressure phenomenon are discussed.

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SIMULTANEOUS CALIBRATED RECORDING OF DISPLACEMENT, VELOCITY, AND ACCELERATION IN BALLISTOCARDIOGRAPHY

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IN THE development of the ballistocardiograph as a useful clinical tool, the motion of the body due to ejection and flow of blood must be studied thoroughly from the point of view of the transfer characteristics of the transducer. This must be done before adequate biophysical analysis of the human body can be undertaken.

Calibrated instrumentation is of vital importance so that qualities of motion can be expressed as absolute units. In this way results can be obtained that are comparable from one person to another, and research development can be attempted on a quantitative basis.

In a previous paper[2] the use of a calibrated bar magnet velocity meter has been described so that the velocity of body motion can be translated to absolute units. From this type of instrumentation a bar magnet velocity meter has been constructed that has sixty-five times the signal output of the earlier model instrument. This great increase in signal is utilized to convert a velocity signal to displacement (integration) and acceleration (differentiation). In order to insure uniformity of response with frequency down to 0.2 cycles, a loss of more than 95 per cent of the velocity signal is involved in integrating the velocity signal to displacement. Similarly, in order to insure uniformity of response up to a frequency of 20 cycles, the loss in signal in differentiation is in the order of 90 per cent or more (acceleration).

INSTRUMENTATION

The bar magnet velocity meter is a voltage generator made up of a coil of wire and a cylindrical bar-magnet of Alnico V. The coil is wound of fine insulated wire in the order of a hundred thousand turns. The magnet has an aspect ratio (length to diameter) of about 15. The coil is also proportioned so that its length to average diameter is high. This design arrangement is planned to give a reasonably wide range of placement of magnet in coil over which good linearity of input motion to output signal is yielded. The linearity range achieved with the instrument herein described is about three-eighths inch.

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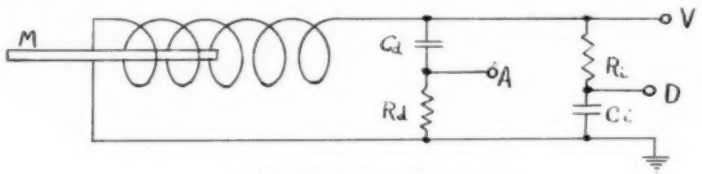
In use a magnet pole is positioned at approximately the axial center of the coil, with the other pole of the magnet external to the coil. The magnet is fastened to a board which is placed across the shins of the subject, and the coil is fastened to the platform on which the subject is resting (Fig. 1). Relative motion between the coil and magnet thus results in an induced voltage in the coil. This signal is proportional to the velocity of the motion since the coil-magnet combination is a velocity transducer. Signals proportional to the acceleration and displacement of the relative motion are produced by parallel differentiating and integrating networks connected across the output of the velocity coil. Thus recordings of velocity, displacement, and acceleration can be made simultaneously. The circuit diagrams are illustrated in Fig. 2.

The frequency amplitude response characteristics of this ballistocardiograph and its networks are shown in Fig. 3.[3]

Fig. 1.—Photograph of attachment of magnet to patient and placement of the bar-magnet in the coil.



RdCd = 0.0005 sec., RiCi = 4.5 sec.

A, acceleration pick-off, D, displacement pick-off, V, velocity pick-off.

Fig. 2.—Circuit diagram of the integrating and differentiating bar-magnet velocity meter.

METHOD OF CALIBRATION

In order to obtain a satisfactory calibration of the ballistocardiograph, a direct mechanical means was used. Since this instrument yields three different signals (one which describes the displacement, one for velocity, and another

which pictures the acceleration of the human body under examination) it is desirable to effect a simultaneous calibration of all three outputs. A modified Atwood machine was arranged so that the magnet was nearly counterbalanced by a weight fastened to the opposite end of the cord which was led over the pulley. By selection of the counterweight, the acceleration of the magnet may be controlled so that a suitable tracing can be obtained. The coil of wire was positioned so that the path of fall of the magnet was lined up with the core of the coil. The

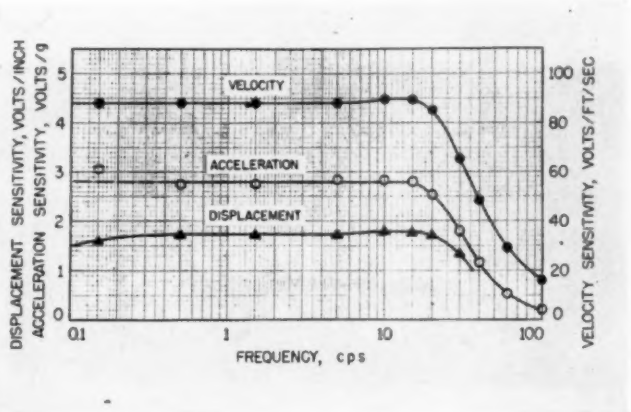


Fig. 3.—Frequency amplitude responses of displacement, velocity, and acceleration.

magnet was then set so that its motion in dropping would be limited to that section of the coil which had previously been determined to be its linear range (that region of the coil where the voltage output is proportional to the velocity of the magnet relative to the coil and independent of its position relative to the coil). This is shown in Fig. 4.

With the output of the coil connected to a suitable recorder (for our purposes we used a Sanborn Polyviso recorder), a tracing can be obtained which can be related to a definite displacement, velocity, and acceleration of the magnet. Since the acceleration of a body is proportional to the force acting on the body and since the effective force acting on the magnet is due to the difference between the weight of the magnet and of the counterweight, the accelerating force therefore is constant and gives constant acceleration to the magnet when it drops. Further, when the acceleration of a body is constant, its velocity is proportional to time. Displacement of the magnet is directly measurable, and the recording can be cross checked by integrating the velocity of the magnet fall. The product of the average velocity and the time throughout which this average velocity applied gives displacement.

A. *Displacement.*—Since the magnet was allowed to drop through a known distance, a calibration of the displacement trace is directly obtained.

In calibrating the ballistocardiograph described in this paper, the displacement used was one centimeter. The sensitivity of the recorder as related to the input of the preamplifier was 100 millivolts for 5.4 chart millimeters. This was obtained by setting the one millivolt standardizing voltage to give 5.4 mm. of chart ordinate and then setting the attenuator to X-100. From the above the number of millivolts per centimeter of displacement can be obtained. During actual

ballistocardiographic recordings on a live subject, it was found necessary to attentuate the recordings by a factor of four instead of a factor of 100. By standardizing at one millivolt for 12 chart millimeters and attentuating by four as above, a sensitivity of .0050 mm. of displacement per chart millimeter (.00020 inch of displacement per chart millimeter) was obtained. A typical IJ complex under these conditions gave a chart displacement of 20 mm. which corresponds to a body displacement in the order of .004 in. in young normal adults.

A note of caution should be observed in checking the displacement calibration. Since the calibration is made through the alternating current preamplifier, the rate of drop of the magnet should be varied until a stabilized value of displacement is achieved. This minimizes the effect of the drop off of response of alternating current amplifiers at very low frequencies. The recorder used has good frequency response down to about one-third of a cycle per second.

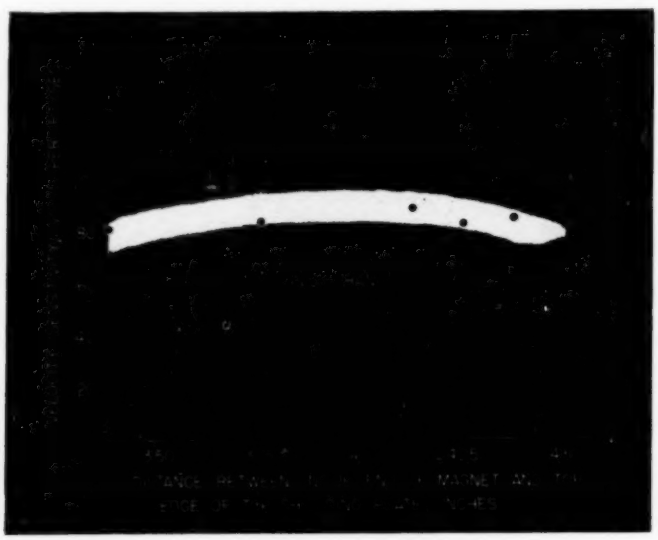


Fig. 4.—Chart showing sensitivity of bar-magnet velocity meter versus relative position of coil and magnet.

B. *Velocity.*—The velocity of the magnet during the drop can be computed since the displacement is known by measurement and the acceleration is constant. The velocity at start is Vo = O, the peak velocity is V = pk, and the average velocity is V = avge.

$$\text{V avge} = \frac{\text{V pk} - \text{Vo}}{2} = \frac{\text{V pk}}{2} = \frac{\text{displacement}}{\text{time}}$$

The time can be determined since the chart speed is known. This allows the average velocity to be established and consequently peak velocity. The values thus obtained compare closely with the formula $X = \frac{Sd}{A}$ in which

X = mm./sec. velocity per chart millimeter
S = chart speed in millimeters per second
d = displacement of magnet in millimeters
A = area under velocity calibration curve in square millimeters

This formula* and its verification were presented in a previous paper.[2]

Due to the relatively high voltage output of the coil, the velocity tracing was made without the preamplifier and by leading the velocity signal directly into the direct current amplifier of the Sanborn Polyviso recorder. By setting the sensitivity of the recorder to one millivolt for 7.9 millimeters, and the attentuator at X-4, a velocity sensitivity for this ballistocardiograph of .10 mm./sec. per chart millimeter was obtained.

*With the use of this velocity calibration, an independent check on the acceleration calibration can be obtained from the electrical calibration of the differentiator.

C. *Acceleration.*—The acceleration of the magnet can be determined by the formula $A = \frac{V}{T}$ where A is acceleration in millimeters per second per second, V is velocity in millimeters per second, and T is time in seconds. By taking V as the peak velocity determined in the velocity calibration, a reasonably good calibration can be obtained. A good cross check can be computed by taking the displacement, computing peak velocity, and then computing A as above. By adjusting the voltage sensitivity of the recorder at 5 millimeters per 4 millivolts a value of 3.2×10^{-4}g or 3.0 mm. per second per second per chart millimeter of amplitude was obtained (lg = 980 mm. per second per second). A typical JK acceleration complex thus indicated a value of 60 millimeters per second per second in a young normal adult.

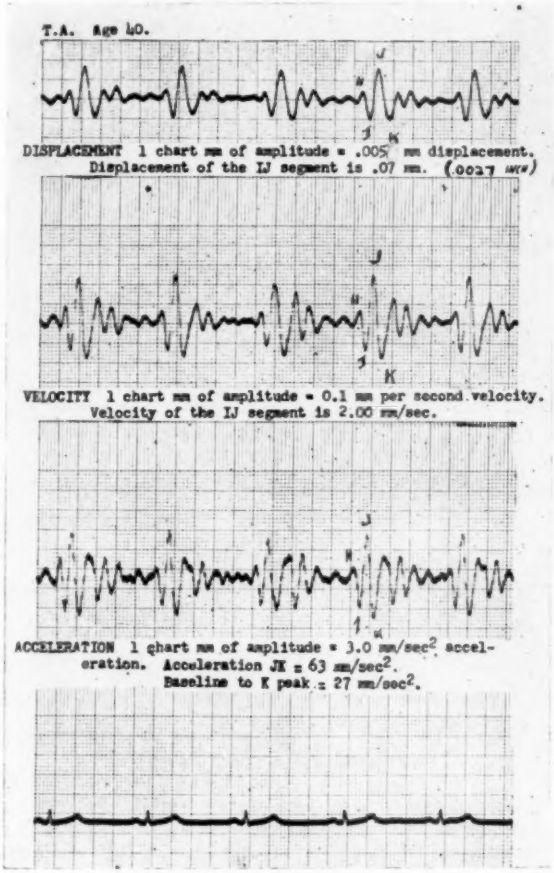


Fig. 5.—Simultaneous calibrated recordings of displacement velocity and acceleration in a 40-year-old normal man.

CASE REPORTS

CASE 1.—A 40-year-old normal adult man. The illustration shows the amplitudes of displacement velocity and acceleration with application of the calibration factors (Fig. 5).

Note that the velocity curve is 90 degrees out of phase and ahead of the displacement curve. The velocity peak represents the peak velocity of the IJ displacement segment. At the peak of the J displacement the velocity curve has returned to the base line. Thus the velocity J and K peaks represent the peak velocity of the displacement IJ segment and the displacement JK segment.

The acceleration curves are 90 degrees ahead and out of phase with the velocity curves and 180 degrees ahead of the displacement curves. The acceleration J wave represents the peak deceleration of the velocity IJ segment and represents the deceleration component in the motion from the H peak to I peak in the displacement curve. The distance from the base line to the peak of K wave in the acceleration curves represents the peak acceleration from the base line to peak of J wave in the displacement curve and becomes an extremely sensitive index of alteration in coronary heart diseases.

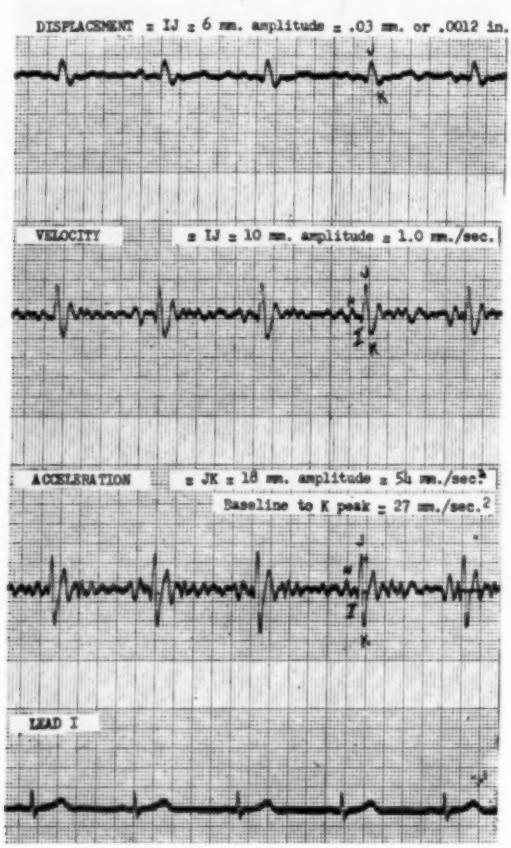
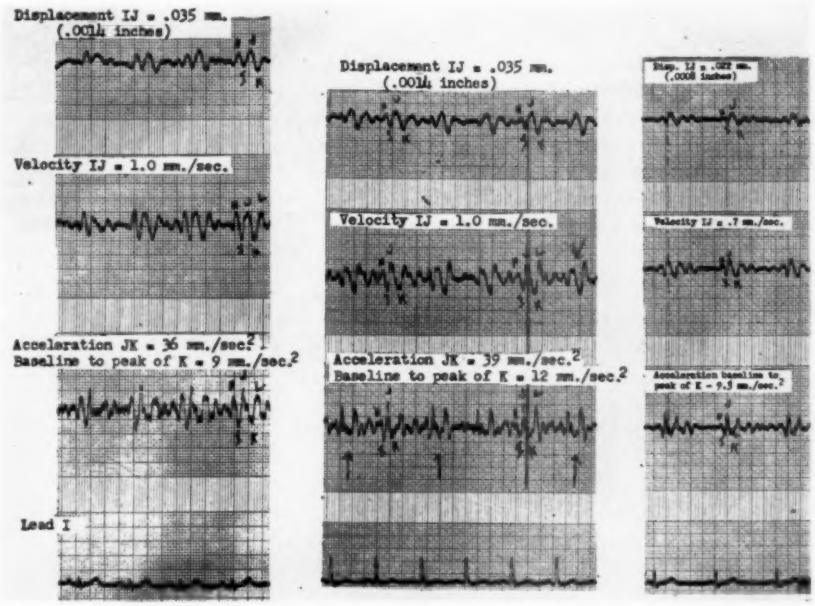


Fig. 6.—M. W. Blood pressure 130/80. No evidence of cardiovascular disease. Simultaneous calibrated recordings of displacement, velocity, and acceleration in a normal 57-year-old woman. Note the high frequency component in the velocity and acceleration HI segments. This occurs in most normal older people and may be due to deceleration of blood in the pulmonary circulation.

CASE 2.—A normal 57-year-old woman. Figure 6 illustrates the changes in amplitude that take place with advancing age. The amplitudes of the case are about average for normal people in this age group. This is an extremely important consideration in ballistocardiography as errors in technique will yield abnormalities in normal older people if ambient vibrations are coming from the recording system. This is caused by a decrease in the signal-noise ratio, and since the older people have low signals they will seemingly have abnormal curves if great care is not taken to provide for ballistic measurements taken in an environment free of environmental ambients exclusive of the body per se. It is probable from the literature published to date that many normal older people are recording spuriously abnormal ballistocardiographs due to this factor in direct ballistic measurements. There is no evidence of ambient vibration in Fig. 6.

It should be noted that the displacement curve is of low amplitude compared to that of young normal adults (.03 mm. or .0012 inches compared to .05 to .1 mm. in young normal adults). The reason for this is obscure at present. The older normal subjects seem to show a higher coefficient of body damping than do young people. It is possible that changes in tissues with age may be responsible. Also, it may be that the older person has less oxygen requirement per body weight and thus requires a smaller total volume of blood per minute. Whatever the explanation may be, the amplitudes of displacement curves get smaller, and the IJ displacement slope is changed. This is reflected on the acceleration curves as amplitudes resembling the younger normal subjects. It may be possible to study the older age groups more advantageously from the viewpoint of acceleration so that changes in the displacement curves can be more readily understood.



A. *B.* *C.*

Fig. 7.—Simultaneous calibrated recordings of three cases of proved coronary artery disease, healed and ambulatory. *A*, 42 years old; *B*, 44 years old; *C*, 44 years old.

Case 3.—R.S. Age 42. Fig. 7, *A*. Healed myocardial infarction. This man had a typical history and electrocardiogram of a posterior myocardial infarction with large Q waves on Leads II, III, and aV_F with inverted T waves. Note the early M patterns on both displacement and velocity curves. The acceleration K waves have become slurred and of low amplitude. No symptoms are present other than moderately severe fatiguability.

Case 4.—L.C. Age 44. Fig. 7, *B*. Healed posterior infarction. The displacement curves look quite normal except for low amplitude. The velocity curves show low peak velocity with flattening of J peaks. The acceleration curves show the loss of amplitude from the base line to peak of K wave which represents the motion in the displacement curve from the base line to the peak of the J wave. Recovery has been excellent and no symptoms referable to the cardiovascular system.

Case 5.—A.L. Age 44. Fig. 7, *C*. Healed posterior wall infarction. The displacement curve is of low amplitude. Velocity curves show low amplitudes with minimal distortion of form. The acceleration curves show typical changes of coronary heart disease with loss of amplitude from base line to peak of acceleration K. Recovery has been excellent.*

These three cases of coronary disease have been picked because they have shown the closest to normal displacement curves in form in twenty-six cases since

*Courtesy of the Medical Department, Bolling Field Hospital.

this instrument has been used. All of these cases have shown marked abnormality in the acceleration curves which is more difficult to see in the displacement curves. Cases 4 and 5 had shown ballistocardiograms that had been interpreted as normal with commercial Dock[1] type ballistocardiographs before referral to our laboratory.

CASE 6.—C.D. Age 21. Fig. 8. Rheumatic fever at the age of 10 years. Complained of dyspnea and precordial pain on exertion and nosebleeds. Blood pressure, 150 to 190 mm. Hg. systolic per 100 mm. Hg. diastolic in arms. Blood pressure in lower extremities was 90/50 mm. Hg. Electrocardiogram showed left ventricular hypertrophy. Roentgenogram showed typical rib notching with suprasternal pulsations and a definite bruit. Systolic and diastolic murmurs were heard at aortic valve area. A diagnosis of coarctation of the aorta and aortic insufficiency was made on a clinical basis.

The displacement curves show evidence which we believe is indicative of coarctation namely the short K wave in relation to a high amplitude IJ segment. Note that the displacement IJ segment is 0.0034 in. (0.085 mm.). Also, the ratio of the JK segment to the IJ segment is 82 per cent which is low. In our experience this ratio seems to be good evidence of aortic obstructions as this type of wave ratio with calibrated instruments has never occurred in over 200 normal subjects to date. However, we have found occasional cases of coronary disease showing this type of low JK to IJ ratio, but never with an IJ amplitude over 0.0016 inches which we believe is evidence of the importance of calibrated instrumentation.

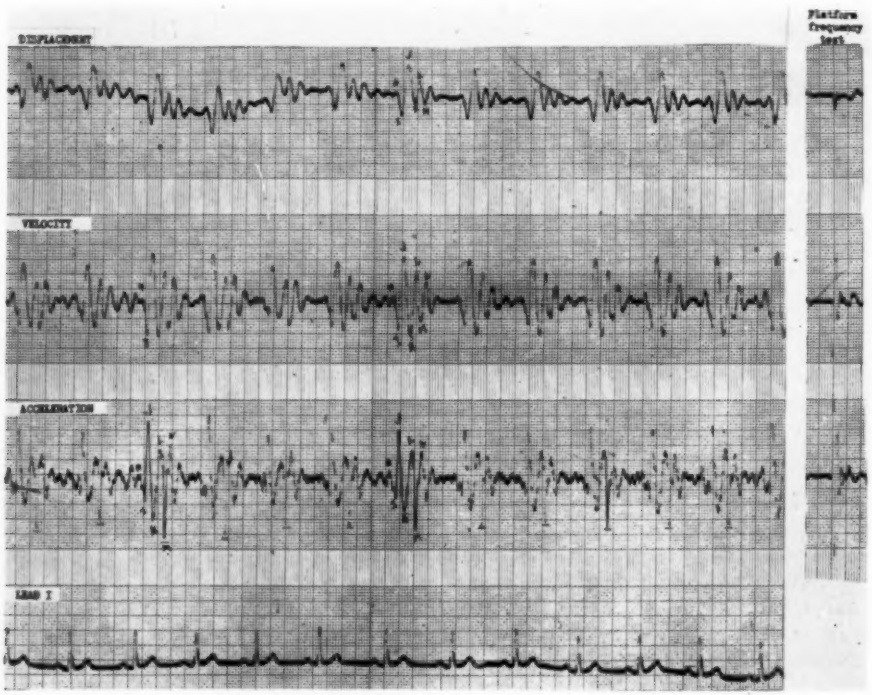


Fig. 8.—Simultaneous calibrated recordings of a 21-year-old man with aortic coarctation, located one centimeter below the left subclavian artery, and aortic insufficiency. Note the short K wave in the displacement curve which may be evidence of coarctation. The acceleration curve looks entirely different and shows a deep acceleration amplitude starting at the peak of the acceleration L wave.

The lowest ratio of the displacement JK segment to the IJ segment with an amplitude of 0.0016 inch and over was 90 per cent in the normal group. The lowest displacement JK of IJ ratio in our normal standard group with an IJ of 0.0030 inch or over was 106 per cent. Thus, we believe that calibrated instruments will be of great value in this type of measurement. The acceleration curves show a marked deviation from normal starting at the peak of the acceleration

L wave. The extremely high amplitude L to M complex probably represents the marked acceleration due to a combination of coarctation and aortic insufficiency. If the velocity curve only were recorded it would be difficult to show evidence of either the coarctation or the aortic insufficiency.*

DISCUSSION

In the recording of body motions in ballistocardiography, adequate attention has not been given to the transfer properties of various transducers, frequency response characteristics of transducers, and the requirements of the measurement of motion in a two degrees of freedom system.

The first degree of freedom as represented by the body mass and coefficient of elasticity of the skin and subcutaneous tissues needs much investigation from the biophysical point of view. The second degree of freedom is represented by the skin-transducer mass placed on the legs. Fundamentally to transfer motion accurately from the body, the natural frequency of the skin-transducer system must be far removed from the natural frequency of the body, and the damping in the second degree of freedom should be known. The second degree of freedom is readily amenable to sound biophysical analysis and obeys the simple physical law of frequency $= \sqrt{\frac{k}{m}}$ where k is the coefficient of elasticity of the skin and m is the mass of the transducer on the legs.

Studies of transducer and weight factors on the skin have been completed. The use of a simple segment of an elastic stocking on the legs to raise the frequency of the transducer mass above 15 to 20 cycles has been validated.[4] Calibrated instruments are useless unless the technical factors of accurate motion measurement are understood. The elastic stocking is used to raise the natural frequency of the magnet and mounting to at least four times the natural frequency of the body (4 to 7 cycles).

It must be emphasized that the indiscriminate use of individually calibrated instruments can lead to the same type of difficulty as the use of uncalibrated instrumentation. Calibrated instrumentation requires an understanding of the operation and limitations of the complete system, the instruments as well as their mounting on the body.

A great difficulty today in direct ballistocardiography seems to be the lack of understanding of ambient vibration interference. In the young person with high amplitude signals, the ambient vibration is difficult to see unless acceleration curves are used.

In the older people the signal amplitudes decrease and thus ambient vibrations from the tables and buildings become devastating to accurate clinical measurements. In other words the signal-noise ratio has decreased and thus most normal older people show abnormal curves. The tracings on older normal people tend to be obscured or obliterated by the relatively higher noise background. This unfortunately may lead some observers to conclude that all older people give abnormal patterns. It is in the older age groups where high fidelity of recording is so absolutely necessary for clinical interpretation.

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*Courtesy of Department of Cardiology, Walter Reed General Hospital.

SUMMARY AND CONCLUSIONS

1. The construction of an integrating and differentiating bar-magnet velocity meter has been presented.

2. The techniques of calibration and recording of simultaneous tracings of displacement, velocity, and acceleration have been shown.

3. The importance of the skin-transducer mass in the second degree of freedom to record accurately the motion of the body has been emphasized.

4. The measurement of body acceleration has been discussed, and the marked changes from normal in coronary artery disease have been demonstrated.

5. The use of calibrated instrumentation should have great value in ballistocardiography.

Grateful acknowledgment is made to Thomas A. Perls, Ph.D., and C. W. Kissinger, M.S., Physicists, Office of Basic Instrumentation, National Bureau of Standards, who developed the instrumentation as well as the techniques used in this calibration, also, to J. D. Garner, Medical Technician, for his assistance in calibration.

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THE EFFECT OF INDUCED HYPERKALEMIA ON THE NORMAL AND ABNORMAL ELECTROCARDIOGRAM

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PREVIOUS studies of the effects of hyperkalemia on the electrocardiogram have been of two general types: (1) those describing the electrocardiogram abnormalities associated with hyperkalemia,[1-24] and (2) those studying the effects of hyperkalemia on pre-existing electrocardiogram abnormalities.[21,22,25-31] The present studies belong to the second type and are an attempt to study more systematically than has been done before the effects of induced hyperkalemia on several of the recognized types of T-wave abnormalities in the human electrocardiogram.

Sharpey-Schafer, who was the first to approach this problem, concluded that the T-wave inversion caused by myocardial infarction became more marked, the T-wave inversion associated with ventricular preponderance became upright, and the T-wave abnormalities of myxedema reverted to normal with increases in serum potassium.[25,26] Of subsequent reports two have confirmed[22,28] and one not confirmed[31] these observations. One of the reasons for conflicting results in these and other studies of the effects of potassium on the electrocardiogram has been the use of differing and often inadequate methods for evaluating the T-wave changes. Indeed, in some studies the conclusions have been based upon T-wave contour variations in only a single lead, and there has been no way after the administration of potassium to identify changes in the T waves which might be due to shifts in heart position or variations in precordial electrode location rather than the potassium.

Recently a method has been described for analyzing the conventional electrocardiogram by treating the QRS and T deflections on the various leads as measurements of single central QRS and T-electrical forces or vectors. By using appropriate axis systems the information in the various limb and precordial leads is consolidated and expressed in terms of the magnitude and direction of mean spatial vectors generated during the QRS, S-T, and T intervals. The method is based upon sound electrophysiologic principles and is more rational and objective than are methods based upon patterns of the deflections in the various leads. This is especially true in comparative studies such as the present one where the electrocardiograms before and after the administration of potassium in a given

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patient are to be compared. What might be called minor changes in the T waves of one or another lead, which are difficult to evaluate by other methods of interpretation, are by this method studied quantitatively by measuring the direction and magnitude of the electrical force responsible for the T waves in all the leads. This gives considerably more information and greater accuracy than do other methods of interpretation. In addition, with this method it is possible to differentiate the changes in the T waves which are due to alterations in either body or heart position from the changes which are due to the potassium. These aspects of the method, as well as its validity and experimental background, are discussed in greater detail elsewhere.[33,34]

METHODS

In the present study a number of persons representing each of seven recognized types of T-wave abnormality were studied. Additional records of several of these types were obtained from previous studies by others when the clinical data and published electrocardiograms were adequate. In each patient tracings were obtained before and after the administration of the potassium and studied for the changes in magnitude and direction of QRS, S-T, and T vectors by the method previously described.[32,33] In some of the records obtained from the literature, only limb lead tracings were published and in these only the frontal plane characteristics of the vectors could be studied. Electrocardiograms failing to show a definite potassium effect as evidenced by a change in either the magnitude or direction of the T vector were excluded from the study as were also those showing interventricular conduction defects with secondary T-wave changes as a result of the hyperkalemia. Space does not permit the inclusion of the vector diagrams made before and after the administration of potassium in each of the patients studied, and only representative patients of each type will be shown.

With the majority of the patients potassium chloride dissolved in approximately 150 c.c. of fruit juice was administered orally in a single dose. Early in the study results from graduated doses of potassium salts given on separate days indicated that amounts less than fifteen Gm. failed to produce significant electrocardiogram changes, and this was the minimum dose used for all persons reported in this series. In a large percentage of patients electrocardiographic tracings were taken at thirty minute intervals for two hours or until maximal effects were observed. Conventional limb and precordial leads were recorded in all instances except in some of the tilt studies where only the three standard limb leads were recorded. In a few subjects additional chest V-leads were taken to define the changes more clearly. Toxic effects are described later. Patients with severe renal disease were excluded from this study because of the known toxicity of potassium in the presence of severe renal disease.[8,10,11,14] Serum sodium, potassium, and hematocrit values were determined before and after the potassium in many of the cases. Head-up tilt experiments were performed on a conventional tilt table with the subjects actively supporting themselves. The subjects were held at each tilted position (30 degrees, 45 degrees, 60 degrees) for three minutes before the electrocardiogram was recorded.

RESULTS

1. *The Effects of Potassium on the Normal Electrocardiogram.*—In ten young adult men with normal electrocardiograms and no clinical evidence of heart disease there occurred uniformly an increase in the magnitude of the mean spatial T vector without significant change in its direction following the administration of potassium. In other words the angle formed by the mean spatial QRS and T vectors remained normal. This observation is supported by the many reports in the literature of the effects of hyperkalemia on the normal electrocardiogram.[9,13,14,16,18,29] No significant alterations in the S-T segments or duration of the Q-T interval were observed. A U-wave caused by a vector which was usually parallel to the mean spatial T vector was occasionally seen. Typical effects of potassium on the T vector in the normal subject are seen in Fig. 6.

2. *The Effects of Potassium on the Electrocardiogram in Myocardial Infarction.*—The effects of potassium administration on the S-T and T-force abnormalities of myocardial infarction have been studied in seven persons: three from previous reports by others[25,31] and four from this laboratory. The results in a typical patient are shown in Fig. 1. In all patients there was a characteristic clinical story of myocardial infarction and in all but one typical QRS, S-T, and T changes of myocardial infarction had taken place. In one there was no diagnostic QRS abnormality, but the clinical picture and S-T and T changes were characteristic of myocardial infarction. All patients were studied during convalescence while a measurable injury current was still discernible in the S-T segment.

In all patients potassium administration caused the mean spatial T vector to become increased in magnitude with little or no change in direction; that is, the QRS-T angle remained abnormal. In two patients the components of the mean S-T vector which are generated toward the end of the S-T interval were also increased in magnitude without alteration in direction, causing the mean S-T vector to be increased in magnitude. In short, potassium tended to augment the characteristic S-T and T-contour changes of myocardial infarction in these patients. These effects of potassium on the electrocardiogram of myocardial infarction were first pointed out by Sharpey-Schafer[25] and have also been seen in experimental myocardial infarction following potassium administration.[30]

3. *The Effect of Potassium on the Electrocardiogram Abnormality of Left Ventricular "Ischemia."*—The effects of potassium administration on the T-vector abnormality of left ventricular "ischemia" have been studied in ten patients, and one additional report was obtained from the literature.[3]

The syndrome of left ventricular ischemia is used here as a strictly electrocardiographic entity. It is characterized by a normal QRS loop, an abnormally directed mean spatial T vector which points away from the left ventricle (and hence an abnormally wide QRS-T angle of usually 90 to 100°), and the absence of a measurable S-T vector.[32,34,37] Although left ventricular ischemia is an electrocardiographic term, the subjects selected for study were those in whom the electrocardiogram abnormality was accompanied by a clinical picture of myocardial disease. Seven of the ten subjects had clinically evident arteriosclerotic

heart disease. One patient had no clinical heart disease, but was 66 years of age, and chronic coronary vascular disease was likely. Another patient was a 42-year-old white man with chronic congestive heart failure and a clinical diagnosis of chronic rheumatic myocarditis, and another patient had acute tuberculous pericarditis.

The effects of the potassium in a typical case are shown in Fig. 2. In the patient with pericarditis the small S-T vector increased in magnitude while the T vector decreased in magnitude but remained abnormally directed following the administration of potassium. In all the other subjects potassium caused the mean T vector to increase in magnitude with little or no change in direction, so that the QRS-T angle remained abnormal.

4. *The Effects of Potassium on the Electrocardiogram of Left Ventricular Strain.*—The effects of potassium on the S-T and T abnormalities of left ventricular strain have been studied in twelve persons; six from previous reports by others[9,12,25,31] and six in this laboratory. The criteria used in this study for the electrocardiographic diagnosis of left ventricular strain consist of a QRS-T angle of nearly 180 degrees and a definite S-T vector which is relatively parallel with the T vector.[32,34] Generally, electrocardiographic evidence of left ventricular hypertrophy is also present; that is, the mean QRS vector is of greater than normal magnitude and is usually directed more leftward and posteriorly than in the normal subject. In the six subjects studied in this laboratory hypertensive cardiovascular disease was responsible for the left ventricular strain electrocardiogram abnormality. The results in a typical patient are presented in Fig. 3.

In all twelve cases potassium caused an increase in the magnitude of the mean spatial T vector, but little or no change in magnitude or direction of the S-T vector. Occasionally it altered the T vector slightly in direction; however, no instance was observed in which the angle formed by the mean QRS and T vectors became normal.

Sharpey-Schafer concluded from his studies that T-wave abnormalities caused by left ventricular preponderance became corrected after potassium administration.[25] However, careful study of the electrocardiograms of the two published reports reveals that in one patient there was a change in the direction of the mean T vector following potassium administration but the QRS-T angle remained definitely abnormal, and in the other patient an intraventricular conduction defect with secondary T-vector changes followed the potassium administration.

Bryant reported findings similar to those of Sharpey-Schafer but published no electrocardiograms.[28] Levine and associates[22] have reported a group of patients with uremia in whom the T-wave abnormalities of left ventricular hypertrophy disappeared with the onset of hyperkalemia. In the only patient whose tracings were shown, the initial electrocardiogram showed an abnormally directed T vector but no S-T vector, and as uremia progressed with development of potassium intoxication, the mean T vector became relatively normal in direction. Similar reversion of an abnormally directed T vector to normal with the onset of hyperkalemia in a uremic patient was published by Keith and Burchell,[19] but the control tracing did not resemble left ventricular strain. Uremia is associated with

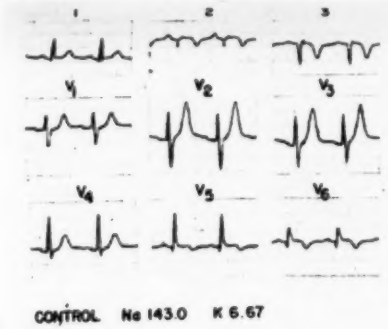

Fig. 1.

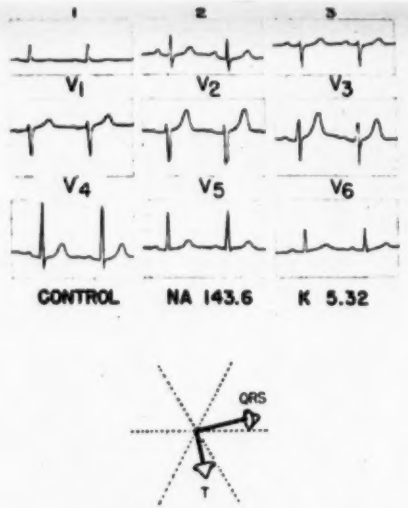

Fig. 2.

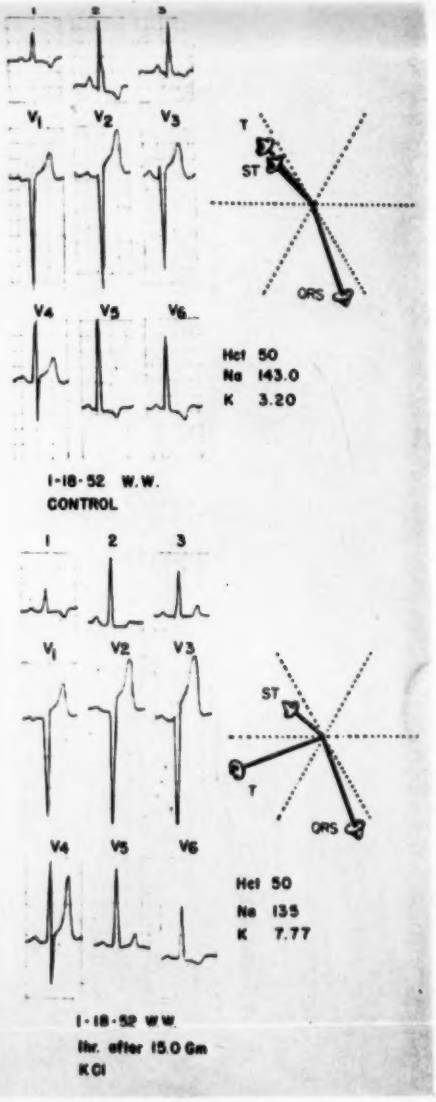

Fig. 3.

Fig. 1.—44-year-old man; acute posterior myocardial infarction three weeks previously. 15.0 Gm. KCl orally. Fig. 2.—66-year-old man; no history or clinical evidence of heart disease. Electrocardiogram of left ventricular ischemia. 15.0 Gm. KCl orally. Fig. 3.—36-year-old man with severe essential hypertension but n- heart failure. 15.0 Gm. KCl orally.

a host of metabolic and hemodynamic disturbances which in themselves may result in T-vector abnormalities resembling those seen in left ventricular strain, as will be discussed later. Accordingly, it is difficult to be confident that the T abnormalities in these patients were due solely to ventricular hypertension. This consideration may account for the discrepancy between the observations reported by Levine and associates and the observations reported here.

In addition it is well to remember that abnormal S-T and T vectors of left ventricular strain in patients with hypertension have been noted to occasionally revert to normal following sympathectomy with or without an associated lowering of the blood pressure. Indeed, such changes in the S-T and T vectors of hypertensive patients may occur spontaneously without any hemodynamic or metabolic event to explain the change.

Schlachman and Rosenberg[31] administered oral potassium to a patient with diabetes and hypertensive cardiovascular disease and observed abnormal T waves to become normal. The control electrocardiogram in this patient does not fulfill the criteria for left ventricular strain cited above, and in view of the diabetes this may well represent potassium effect on a metabolic T abnormality.

5. *Metabolic T-Wave Abnormalities.*—The effects of potassium administration on T-wave abnormalities of metabolic origin have been studied in eight patients: two from a previous report by Sharpey-Schafer[26] and six from this laboratory.

In these subjects the electrocardiographic abnormality consists of an abnormally small and/or abnormally directed mean T vector. Prominent U waves and bizarre T loops are occasionally seen in this group. The QRS loop is normal, and no S-T vector is present.[32] Two of the patients had, in addition, an isolated area of T negativity over the left anterior chest. This aspect will be discussed later in the section dealing with isolated T negativity.

It is important to realize that none of the patients in this group had primary cardiac complaints or evidence of primary heart disease. This is a basic feature of this type of T vector abnormality, for the electrocardiogram abnormality itself is not different from that of ischemia. In both groups the sole electrocardiogram finding is an abnormal T vector. To be sure most of the patients in this group had some systemic or generalized disease, but the electrocardiogram was the only cardiac abnormality, and for this reason has been called a metabolic T-vector abnormality. Three of the patients were young adults with well-controlled diabetes mellitus, one had a chronic pulmonary abscess, one was a 36-year-old man receiving antimony for schistosomiasis, and one, illustrated in Fig. 4, had no recognized evidence of disease. The two patients studied from previous literature had myxedema.[26]

In all of this group the administration of potassium caused the mean spatial T vector to become increased in magnitude and changed in direction so that the QRS-T angle became perfectly normal for a few hours. This is in striking contrast with the effects of potassium administration on the ischemia T-vector abnormality described earlier.

It is believed that the T-vector abnormality in this group of patients is representative of that seen in the course of a wide variety of noncardiac illnesses where

transient T abnormalities develop. These transient T changes have often in the past been considered evidence of myocardial involvement or even myocarditis. The T-wave abnormalities described in anemia, anoxia, thyroid disease, nephritis, emetine therapy, sulfonamide administration, hepatitis, and other diseases may well fall into this group. Furthermore, there is a group of individuals who show metabolic T-vector abnormalities, but in whom no disease, cardiac or otherwise, can be detected by the most careful study. Figure 4 is an example of the record of such a patient.

The etiology of these metabolic T-vector abnormalities is not known. Relatively similar T-vector abnormalities are seen in instances of frank hypokalemia such as in familial periodic palsy and with the secondary hypokalemia following chronic over-administration of laxatives.[39] In other circumstances although hypokalemia may be present, additional factors appear to be involved in the production of the T-vector abnormalities. This is evident from studies on patients in uremia,[40] chronic nephritis,[41] and sprue,[41] and patients recovering from diabetic acidosis;[16,42-44] for, in these patients there has been found a relatively poor correlation between the serum potassium levels and the electrocardiographic changes. Finally, there is a much larger group of patients who show this T-vector abnormality, yet have no evidence of potassium deficiency, if the level of serum potassium is used as an index of potassium deficiency.[40] Such, indeed, was the case in the patient illustrated in Fig. 4, who had a normal serum potassium level at the time the electrocardiogram abnormality was present.

6. *Effect of Potassium on Isolated T Forces.*—The effects of potassium administration on areas of isolated T-wave negativity have been studied in seven patients. The syndrome of isolated T negativity has been described elsewhere.[34] In each of these patients the localized character of the area of T negativity of the left anterior chest was confirmed by electrocardiographic mapping of the chest. In none could the electrical force responsible for the T-wave negativity on the left precordium be identified in the extremity leads.

From the standpoint of clinical diagnosis this is a heterogeneous group: one patient (Fig. 5) was a 37-year-old white man with no evidence of heart disease; two patients had transient areas of isolated T negativity following myocardial infarction; two patients had arteriosclerotic heart disease with left ventricular ischemia in addition to isolated T negativity; and two patients had spatial T-vector changes of the metabolic type in addition to isolated T negativity. The electrocardiogram reproduced in Fig. 5 is representative of the effect of potassium on isolated T negativity in this group of patients.

In none of the patients studied was the area of isolated T deformity eliminated following potassium administration. In two patients who had small spatial T vectors of the metabolic type in addition to the isolated T negativity, the increase in magnitude of the spatial T vector following potassium produced upright T waves in the isolated area; however, the isolated abnormality was still apparent as a downward deformity superimposed on the upright T waves in this area. These results are similar to those previously reported concerning the effect of orally administered potassium in two normal subjects having isolated T negativity.[34]

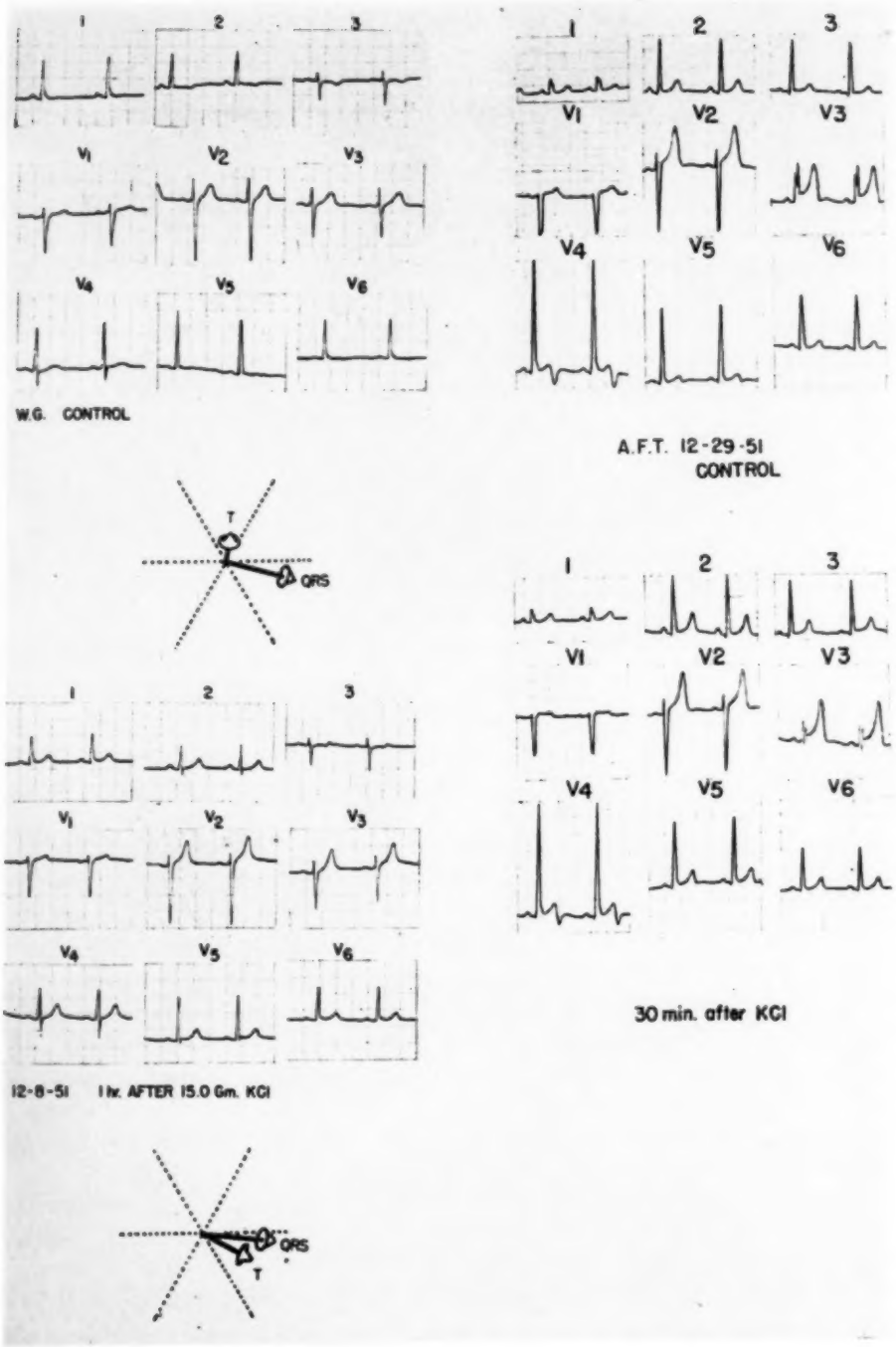

Fig. 4.

Fig. 5.

Fig. 4.—42-year-old man; no history or clinical evidence of heart disease. Electrocardiogram shows "metabolic" T-vector abnormality. 15.0 Gm. KCl orally. Control serum K 4.5 meq./L.

Fig. 5.—32-year-old man with no history or clinical evidence of heart disease. Isolated T-wave negativity at V_4 and V_5. 15.0 Gm. KCl orally.

7. *The Effect of Potassium on Tilt-Induced and Digitalis-Induced T-Vector Abnormalities.*—The effect of potassium on T-vector changes produced by head-up tilting was studied in four normal young adult men who developed rather marked changes in the direction of the mean T vector with widening of the QRS-T angle on tilting. Following control observations in the flat and tilted positions, 15.0 Gms. of potassium chloride were administered orally, and flat and tilt electrocardiograms were recorded at thirty minute intervals. The results are shown in Fig. 6. It can be seen that following potassium administration little, if any, T-vector rotation occurred on tilting and the QRS-T angle remained relatively normal.

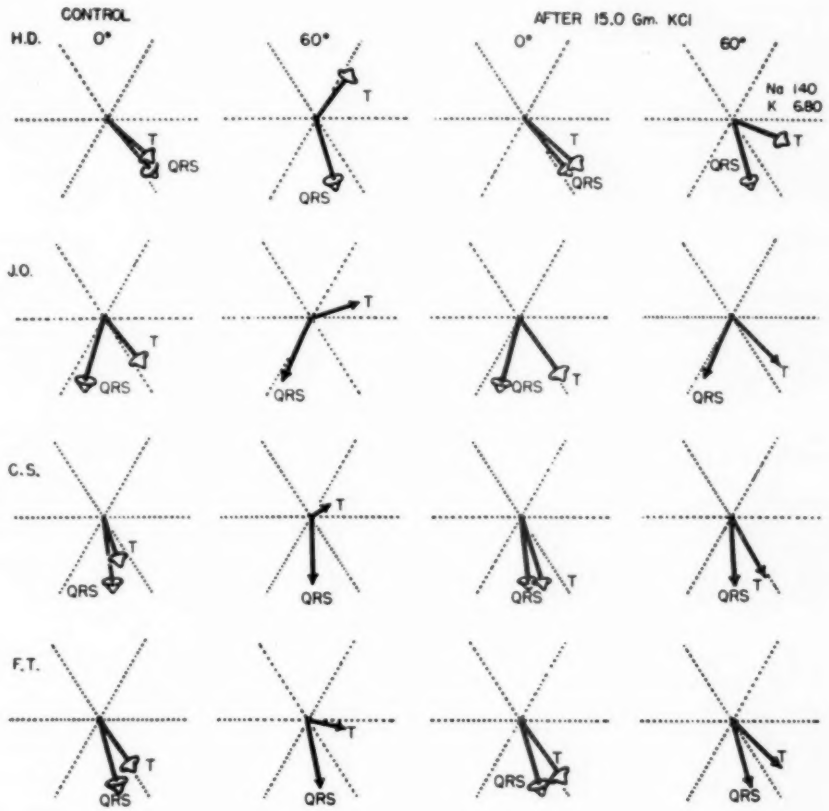

Fig. 6.—Four normal subjects with observations in flat and tilted positions before and after 15.0 Gm. KCl orally.

That tilting and standing upright will produce T-wave changes has been known for many years.[45-51] However, there is no general agreement as to the mechanism of these T changes. Some investigators ascribe the changes to an alteration in contact between the heart and neighboring tissues;[46,47] others have speculated that the changes are due to sympathetic stimulation occurring as a result of either diminished venous return[48] or autonomic imbalance;[49,50] and still

others have attributed it to anoxia of the heart,[52] change in the position of the heart,[45,53] the presence of myocardial damage or heart disease,[54-56] or change in stroke volume and heart rate.[51] Previous studies by the authors have shown that rapid intravenous infusion of saline or Dextran will abolish these T-vector changes produced by tilting for the duration of the infusion, indicating that the T changes are related to hemodynamic alterations.[57] The present studies indicate that potassium also tends to abolish these hemodynamic T-vector changes.

In previous studies in this laboratory digitalis has been found to enhance the degree of T-vector rotation produced by tilting.[34] Subjects who show little or no T-vector rotation on tilting will, following the administration of a dose of digitalis small enough to produce little or no electrocardiogram effect, show much more marked T-vector rotation on head-up tilting.[32,57] These T-vector changes can also be prevented by intravenous infusion of Dextran.[57] Accordingly, these studies with potassium were extended to include a group of normal subjects to whom digitalis had been administered.

Three normal young men were studied. Control electrocardiograms were taken with the patients flat and head-up tilted. Each subject was then given 1.2 mg. digitoxin orally in two or three divided doses. Twelve to twenty-four hours later flat and tilt electrocardiograms were recorded and the patient was given 15 Gm. of potassium chloride orally. Flat and tilt electrocardiograms were obtained at thirty minute intervals thereafter. The effect of potassium on the mean T vectors in these subjects is illustrated in Fig. 7.

In the normal subject small amounts of digitalis reduce the magnitude of the T vector without causing a significant change in its direction. Larger amounts further reduce the magnitude of the T vector and produce an S-T vector opposite in direction to the mean spatial QRS vector.[32] (When potassium is given under these circumstances it increases the magnitude of the T vector without altering its direction and without altering the S-T vector if one is present.) These effects of digitalis as well as its tendency to enhance the T-vector rotation associated with tilting are well illustrated in Fig. 7.

It is important to realize that digitalis alone alters little the direction of the T vector. Accordingly, when the T vector is abnormal in direction in a patient who is receiving digitalis, some other hemodynamic, metabolic, or organic factor must be present in addition to the digitalis causing the abnormal direction of the T vector, although the electrocardiographic effects of these various factors may be enhanced by the digitalis as is the case in these tilt experiments.

In these subjects potassium increased the amplitude of the T vector which had been reduced by Digitoxin and partially or completely prevented the digitalis induced tilt-rotation of the T vector. The S-T interval which was slightly shortened by Digitoxin was not significantly altered by potassium.

The implications of these experiments for the mechanism of the electrocardiogram effect of digitalis will be discussed in greater detail in a later paper. For present purposes this is another instance of a physiologically induced T-vector abnormality which is temporarily blocked by potassium administration.

8. *Untoward Reactions.*—During the course of these studies previously described untoward reactions to the administration of potassium were observed.

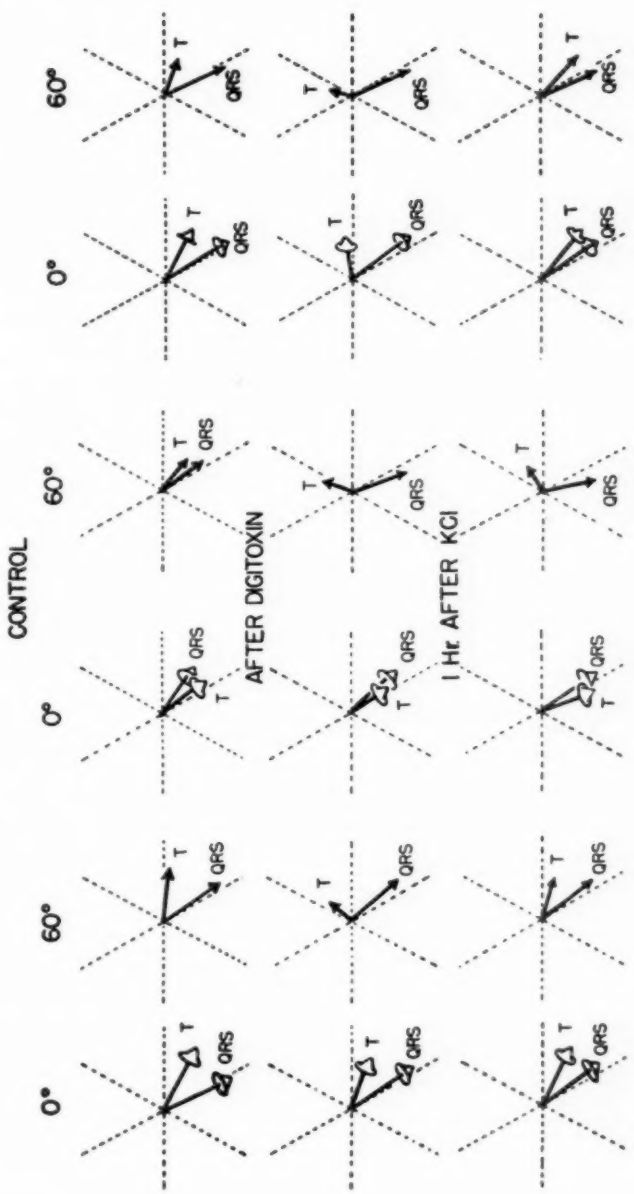

Fig. 7.—Three normal subjects with observations in flat and tilted positions before and after 1.2 mg. Digitoxin and 15.0 Gm. KCl.

These reactions were of two types: (1) gastric irritation due to the oral route of administration of the potassium salt, and (2) symptoms of potassium intoxication. The gastric symptoms of epigastric burning, nausea, and occasionally vomiting were present to a variable degree in nearly all the subjects. Symptoms of potassium intoxication following 15.0 Gm. of potassium chloride orally were observed in approximately one-half the patients but were seldom severe. These symptoms were numbness and tingling of the extremities, of the circumoral region, and occasionally of the entire face, increased perspiration, which in a few patients was profuse, and muscular weakness in one subject.

One patient with rheumatic myocarditis and mild congestive heart failure developed a sinus tachycardia of 140 per minute, became dyspneic, and developed marked nausea, vomiting, and paresthesia. Three patients, all of whom were in the infarct or left ventricular ischemia groups, developed transient substernal pain accompanied by electrocardiographic changes. In one of these subjects, transient S-T segment shifts resembling those associated with angina pectoris occurred. In another, transient enlargement of an isolated T-negative area was observed. In the third subject, a transient intraventricular conduction defect developed. It is of interest that in this third patient the intraventricular conduction defect appeared when the serum potassium level was only 6.10 milliequivalent per liter.

The danger of even fatal effects of potassium administration was appreciated in these studies and experiments with the administration of cautiously increased amounts of potassium salt were undertaken early in the study. Normal subjects, including the investigators, were found able to tolerate as much as 370 milliequivalent of potassium (40 Gm. of potassium citrate) orally in a single dose. Accordingly, it was hoped that doses of 280 milliequivalent of potassium, or less, would be safe for patients with electrocardiogram abnormalities. Nevertheless, one fatality occurred following the oral administration of 200 milliequivalent of potassium (15 Gm. KCl.).

The fatality occurred in a 47-year-old white man who complained of mild exertional dyspnea for nine years and intermittent claudication for three years. There was no history of angina pectoris, chest pain, or congestive heart failure. His cardiac examination was entirely normal with the exception of the electrocardiogram which showed a normal QRS loop but an abnormally directed T vector, producing inverted T waves in Leads I and V_3 to V_6. One hour following the oral administration of 15.0 Gms. of potassium chloride the patient developed short runs of ventricular tachycardia at a time when there were only slight potassium effects as evidenced by increase in T-vector magnitude. Eighty minutes following potassium administration the patient developed fatal ventricular fibrillation. Just prior to the onset of the ventricular fibrillation the T vector was still only slightly increased in magnitude with no change in direction. None of the other electrocardiogram signs of potassium intoxication appeared, such as P-R interval abnormalities, absence of P waves, or intraventricular block. Postmortem examination revealed a marked degree of coronary artery sclerosis with many focal areas of myocardial fibrosis, but no area of frank myocardial infarction.

In summary, the incidence of untoward symptoms following potassium administration was appreciable in the subjects without heart disease, but never were the symptoms alarming. On the other hand in the patients with myocardial infarction, left ventricular ischemia, or congestive heart failure, the reactions tended to be more severe and were fatal in one case. It has previously been noted that patients with congestive failure show a decreased tolerance to potassium administration.[14,21,22] In addition, it has been reported that patients with heart disease and no congestive failure show a diminished ability to excrete administered potassium.[21] Finally, dogs with experimental myocardial infarction usually die of ventricular fibrillation following fatal doses of potassium, whereas normal dogs usually die with ventricular standstill following such fatal doses of potassium. The dogs with the experimental myocardial infarction had lower serum potassium levels at death than did the normal group of dogs.[4]

DISCUSSION

In this study of the effect of administered potassium on various types of abnormally directed T vectors, it has been found that the direction of the T vector is not significantly altered if the abnormality is due to myocardial infarction, left ventricular ischemia, or left ventricular strain. On the other hand, if the T-vector abnormality is the result of hemodynamic factors or systemic metabolic disturbances of a noncardiac nature, the administration of potassium temporarily corrects the abnormality. In the syndrome of isolated T-wave negativity, where abnormal T waves are encountered on the left anterior chest and are not detectable in more remote leads or in the mean spatial T vector, potassium does not correct the deformed T waves whether they are due to heart disease or are encountered in a normal subject.

Since the mechanism by which potassium alters repolarization in the intact heart is not known, it is difficult to explain why it corrects the abnormally directed T vector caused by functional or systemic factors, but not that caused by organic heart disease. The route of administration was not important, for oral and intravenous routes were equally effective. The T-vector rotation produced in certain normal subjects by head-up tilting is corrected either by potassium administration or by rapid intravenous infusions of saline or Dextran warmed to body temperature. This suggests that potassium may have prevented the T-vector rotation by increasing the blood volume in these subjects; however, no change occurred in the hematocrit following the potassium administration. Nevertheless, it remains possible that potassium in some way altered the venous return or cardiac relaxation and diastolic size in these subjects which, in turn, influenced the sequences of repolarization in the myocardium. None of the other types of T-vector abnormalities studied in this report showed significant alteration in the direction of the T vector on rapid intravenous infusion of saline or Dextran. These aspects of the relationship between the electrocardiogram and the mechanical properties of the heart are currently under investigation in this laboratory.

Rotation of the T vector on head-up tilting occurs much more commonly in young adults than in older subjects. The reason for this is also unknown. Occasionally an abnormal T vector caused by hemodynamic factors is seen in the

recumbent position as a constant finding in persons with no other evidence of heart disease and is temporarily corrected by rapid intravenous infusions. An example of this, not included in the present series, was encountered in a twenty-two-year-old man who had been rejected by the army for military service because of his abnormal electrocardiogram. The electrocardiogram had been taken because of a transient irregularity in the pulse which proved to be due to occasional premature ventricular contractions. When studied in the laboratory, his control electrocardiogram showed an abnormally small T vector more anterior and leftward in direction than normal. Following administration of potassium and during rapid saline infusions, his T vector became perfectly normal for the duration of the experiments. His recumbent electrocardiogram has remained abnormal for three years, and no other evidences of heart disease have appeared. This type of T-vector abnormality may be the basis for the T-wave abnormalities described in neurocirculatory asthenia,[58] hyperventilation,[59] anxiety states,[60] and in certain patients who are otherwise perfectly normal.[58, 61]

It is important to realize that completely benign hemodynamic manipulations in normal subjects can produce changes in the T waves which are themselves indistinguishable from the changes produced by organic heart disease. It was hoped that potassium administration might prove to be a clinically practicable method for differentiating these physiologic and metabolic causes of T-wave abnormality from those of a more serious cardiac nature. However, the toxicity of the drug, when given in amounts which produce significant T-vector effects in most subjects, precludes its use unless the potassium is given in cautiously graduated doses and under the most careful supervision. It is to be hoped that some other less dangerous drug will be discovered for this purpose, for unquestionably there are many persons who, because of T-wave abnormalities of uncertain etiology, are wrongly considered to have heart disease with all the unfortunate consequences of such a diagnosis.

SUMMARY

1. The effects of induced hyperkalemia on the normal T vector and various categories of T vector abnormality have been studied.

2. When the T-vector abnormality is due to hemodynamic factors not related to heart disease, or is encountered in the course of some systemic noncardiac disorder, or when it occurs in persons with cardiac defect or other disease, potassium administration will temporarily completely normalize the T vector.

3. When the T-vector abnormality is due to myocardial infarction, left ventricular ischemia, or left ventricular "strain," potassium administration will not correct the T-vector abnormality.

4. The incidence of severe toxic reactions to the potassium, including one fatality, makes it too dangerous for routine clinical use in differentiating functional and metabolic T-wave abnormalities from those associated with significant heart disease.

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THE INCREASED FREQUENCY OF ACUTE MYOCARDIAL INFARCTION DURING SUMMER MONTHS IN A WARM CLIMATE

A Study of 1,386 Cases From Dallas, Texas

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Dallas, Texas

THE SEASONAL and monthly frequency occurrence of acute myocardial infarction has been studied by several investigators reporting data from the northern portion of the United States. Thus Master and associates,[1,2] reporting studies from New York City, Bean[3] from Boston, Wood and Hedley[4] from Philadelphia, Mullins[5] from Pittsburgh, Bean and Mills[6] from Cincinnati, Mintz and Katz[7] from Chicago, and Miller and associates[8] from Rochester, Minnesota, have all found a decreased frequency of occurrence of the disease during summer months and an increased frequency during winter months. Hoxie,[9] reporting from the mild climate of Los Angeles, and Billings and associates[10] from Nashville also found acute coronary occlusion to occur more frequently during the colder months and to be less frequent during the summer.

The present study will introduce data diametrically opposed to the previous studies and will present evidence that in a climate characterized by very hot summer weather, acute myocardial infarction occurs more frequently during the hottest season of the year. No similar studies have previously been reported to show the relative frequency of this disease in the southern United States and its relationship to high daily temperature readings in a hot climate.

METHOD OF STUDY

A survey of all cases of acute myocardial infarction, admitted to three Dallas Hospitals (Baylor University Hospital, Dallas City-County Hospital, and Methodist Hospital), during the years 1946 to 1951 inclusive, was made. The total number of admissions to this group of hospitals during this period was 283,931. In each case the clinical record and electrocardiograms were reviewed and whenever possible the exact time of onset established. The following criteria were employed in judging the accuracy of the diagnosis: (1) A clinical story of chest pain, (2) typical or highly suggestive electrocardiographic findings, (3) clinical and laboratory signs of tissue death compatible with infarction, and (4) whenever obtainable, autopsy confirmation. Each individual clinical record was reviewed and was included if the available evidence justified the clinical diagnosis. De-

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tailed meteorological data were obtained from the Dallas Weather Bureau[11,12] in regard to daily temperature, average monthly maximum and minimum temperatures, relative humidity, precipitation, barometric pressure readings, and studies of wind velocity.

RESULTS

Dallas is an area characterized by very hot summers, with daily maximum temperature readings usually exceeding 95° F. on most days during July and August, and often exceeding 100° F. on many days during these months. The winters are relatively mild, with monthly minimum temperatures for the six-year period of this study during January averaging approximately 35° F., and

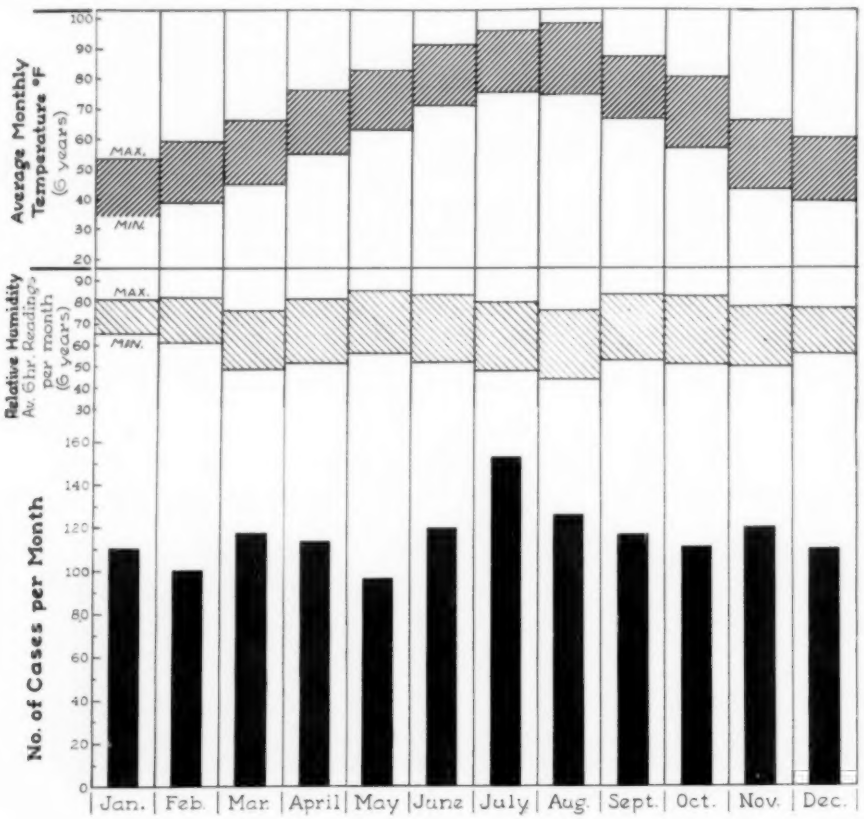

Fig. 1.—Acute myocardial infarction, Dallas (1,386 cases). Admission by months 1946 to 1951 inclusive, with monthly temperature and relative humidity. The greatest number of cases are seen to occur in July and August.

maximum temperatures for this month averaging 54 degrees F. Relative humidity in the Dallas area is also moderate. These meteorological data for various months are presented graphically in Fig. 1. None of the other areas for which similar monthly data concerning the frequency of acute myocardial infarction have been reported (Boston, New York, Pittsburgh, Philadelphia, Chicago, Cincinnati, Los Angeles, Rochester, Minnesota, and Nashville), have summers characterized by such very hot weather. In addition, a majority of these cities,

with the exception of Los Angeles and Nashville, have comparatively severe winters, with much lower average temperatures than those that prevail in Dallas.

During the six year period from 1946 to 1951 inclusive, the diagnosis of acute myocardial infarction was made in 1,666 instances. In 1,386 cases the data appeared adequate to authenticate the diagnosis. There were 340 deaths, an overall mortality rate (including some patients with multiple episodes) of 24.5 per cent. Autopsy confirmation was obtained in 105 cases. The remaining 280 cases were rejected as not justifying a positive diagnosis. The monthly distribution of these cases is shown in Fig. 1. It will be seen that the highest frequency of occurrence of the disease was found in July and August, during the hot summer months.

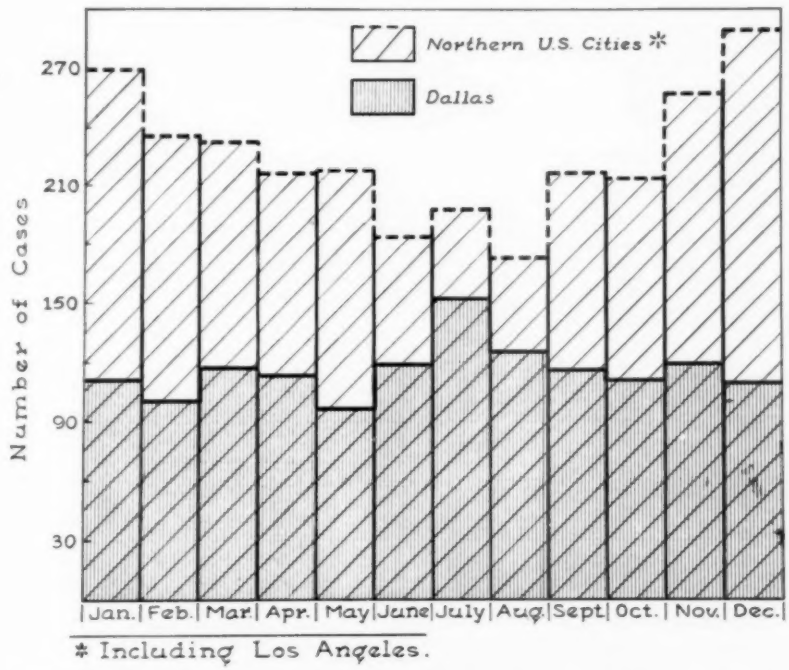

Fig. 2.—Comparison of northern United States cities, including Los Angeles, with Dallas, Texas. The greatest monthly frequency of cases is seen to occur in July and August in Dallas, in contrast to the northern cities, where the largest number of cases appears during the winter months.

When the monthly frequency of occurrence of acute myocardial infarction for the northern cities (including Los Angeles) is compared with that of Dallas, it will be seen that the northern cities show the greatest number of cases in winter months (Table I, Fig. 2). This tendency is definitely different from that prevailing in the Dallas area, where the maximum number of cases is seen in summer months. During the summer period in the northern cities, the number of cases is at a minimum.

When the data are grouped according to three-month seasonal periods (Table II) it will be seen that a similar tendency also prevails, the period of greater frequency of acute myocardial infarction being greatest in the summer season in Dallas. It is also noteworthy that during this hot period, respiratory

TABLE I. MONTHLY OCCURRENCE OF ACUTE MYOCARDIAL INFARCTION—COMPARISON OF VARIOUS U. S. CITIES

AUTHOR	LOCATION	TYPE OF STUDY	YEAR	NUMBER OF CASES PER MONTH												TOTAL NUMBER OF CASES
				JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	
Master et al.	New York	Clinical	1930-1936	**75***	43	48	48	56	44	54	50	46	46	39	63	612
Mullins	Pittsburgh	Clinical	1928-1935	36	**50**	31	28	27	29	24	18	26	29	37	35	370
Wood & Hedley	Philadelphia	Clinical	1932-1934	**19**	13	8	7	11	1	7	4	15	14	**19**	15	133
Mintz & Katz	Chicago	Clinical	1940-1945	47	45	42	42	43	47	41	45	55	51	**61**	53	572
Wm. B. Bean	Boston	Autopsy	1906-1936	20	18	25	**29**	20	13	11	11	28	19	25	27	247
Bean & Mills	Cincinnati	Autopsy	1922-1936	**33**	27	25	22	23	13	19	10	22	25	**33**	26	278
Harold J. Hoxie	Los Angeles	Autopsy	1929-1939	39	39	52	41	38	36	40	35	24	29	42	**70**	485
TOTALS				269	235	232	217	218	183	196	173	216	213	256	**289**	**2697***
Heyer, et al.	Dallas	Clinical	1946-1951	110	100	117	113	96	119	**152**	125	116	110	119	109	**1386**

*The months of greatest frequency of occurrence and the total number of cases are shown in heavy type.

TABLE II. SEASONAL OCCURRENCE OF ACUTE MYOCARDIAL INFARCTION—COMPARISON OF VARIOUS U. S. CITIES

AUTHOR	LOCATION	TYPE OF STUDY	YEAR	NUMBER OF CASES PER SEASON				TOTAL NUMBER OF CASES
				SPRING (March, April, May)	SUMMER (June, July, Aug.)	AUTUMN (Sept., Oct., Nov.)	WINTER (Dec., Jan., Feb.)	
Master & Jaffe	New York	Clinical		268	288	295	**300***	1151
Mullins	Pittsburgh	Clinical	1928-1935	86	71	92	**121**	370
Wood & Hedley	Philadelphia	Clinical	1932-1934	26	12	**48**	47	133
Mintz & Katz	Chicago	Clinical	1940-1945	127	133	**167**	145	572
Billings et al.	Nashville	Clinical	1925-1946	52	49	67	**72**	240
Wm. B. Bean	Boston	Autopsy	1906-1936	**75**	35	72	65	247
Bean & Mills	Cincinnati	Autopsy	1922-1936	70	42	80	**86**	278
Miller et al.	Rochester, Minn.	Autopsy	1946-1949	36	33	31	**43**	143
Harold J. Hoxie	Los Angeles	Autopsy	1929-1939	131	111	95	**148**	485
TOTALS				871	774	947	**1027**	**3619***
Heyer, et al.	Dallas	Clinical	1946-1951	326	**396**	345	319	**1386**
North	Normal deviate $\left(\frac{\Delta}{6}\right)$			−1.1	−4.7	+1.4	+3.8	
Dallas	Normal deviate $\left(\frac{\Delta}{6}\right)$			−1.21	+2.6	−0.1	−1.6	
Odds against difference between the two groups occurring by chance				———	$>10^7$ to 1	———	>20,000 to 1	

*Seasons showing the largest number of cases, as well as the total number of cases, are shown in heavy type.

infection is at a minimum in this locale. By contrast, data from the northern cities (including Los Angeles and Nashville) reveal that the summer season is the period of lowest frequency of this disease. The same striking difference between Dallas and northern cities is also noted for the winter season. Thus, during the winter the northern cities report the greatest frequency of the disease, whereas during the same period in Dallas the fewest number of cases is reported. Moreover, from the size of the samples studied and the results of statistical analysis (Table II) it would appear that this is a real, and not an apparent difference.

DISCUSSION

A perusal of the literature has failed to reveal any report dealing with the seasonal and monthly frequency of acute myocardial infarction from the southern United States in a region characterized by very hot summers. All previous reports from northern cities, as well as Los Angeles and Nashville, concerning the seasonal variation in occurrence of acute myocardial infarction have shown the summer months as the period of least frequency of this disease.[1-10] Similarly, the winter months have been the period during which the greatest number of cases of coronary occlusion have occurred. Secondary periods of relatively frequent occurrence have also been noted in some instances in autumn or spring months. While the exact causes for this variation are not fully known, greater frequency during the winter months has been variously ascribed by other authors to: (1) the increased frequency of respiratory infection,[6,9] (2) an increase in body metabolism in the colder months,[6] and (3) the possible effect of vasomotor reflexes caused by cold weather.[6,22]

In the present study the demonstration that the greatest number of such cases in Dallas have their onset in the hot summer months makes it apparent that other factors are probably operative here different from those that have previously been advanced as causing the greatest number of cases to occur in the winter months in northern cities. It is also apparent that the maximum daily temperatures reached in an area such as Dallas in the summer are much higher than those prevailing in cities previously reporting such data. That respiratory infection is not an important causative factor in the summer months in Dallas is evident, since such infection is at a minimum in this area during this period. Similarly, an increase in body metabolism seems unlikely during this period, since total metabolism has been shown to be relatively depressed by hot weather.[13-16]

The exact cause of the increased number of cases in the hottest portion of the year is unknown. It appears probable, however, that the profound physiologic adjustment that the patient must make to preserve a constant body temperature exerts a considerable strain on the organism and may act as an important precipitating factor of acute myocardial infarction. The humidity is relatively moderate in the Dallas area (Fig. 1) and does not appear, from these studies, to be a stress factor of great importance in this region. It should be further noted, however, that mild heat exhaustion is a comparatively frequent clinical occurrence in Dallas.

It should be remembered that the adjustment to such a hot climate causes an increase in cardiac work, often with increased cardiac output,[16-19] associated

with an increase in blood volume[20,21] and the deviation of a larger portion of the circulation blood volume through the skin to promote heat loss. Arterial blood pressure has been shown to decrease under these conditions, and peripheral resistance to fall.[16-22] Fluid and salt loss through the skin is very large, and if not replaced may lead to a decrease in extracellular fluid and plasma volume.[23-25] With such profound circulatory alterations it is readily apparent that normal physiology is greatly disturbed. Patients predisposed to vascular injury by virtue of pre-existing coronary arteriosclerosis might possibly develop acute myocardial infarction under these conditions. It is possible that in some instances heat exhaustion was a factor predisposing to the development of acute myocardial infarction in some but by no means all patients. However, frank heatstroke with hyperthermia was not seen in this group of patients who had developed acute myocardial infarction. The possible occurrence of a thrombogenic state (with exposure to such a hot environment) with alterations in coagulability of the blood[22,26,27] is also remotely possible, though unproved. Irrespective of the exact factors at work, very hot weather would definitely appear to be a predisposing or precipitating factor of considerable importance in the occurrence of acute myocardial infarction.

SUMMARY

The seasonal and monthly frequency of occurrence in a series of 1,386 cases of proved myocardial infarction is reported from Dallas, Texas. The greatest number of cases occurred in the summer months, and the lowest number of cases in the winter months. No previous data from the United States have been reported concerning the seasonal variation in occurrence of this disease in a hot climate. The increased summer frequency of this illness is entirely different from previous reports from northern United States cities where the greatest number of cases have been found to occur during the winter months. The importance of very hot weather as a precipitating or predisposing factor in acute myocardial infarction is discussed.

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THE INCIDENCE OF MYOCARDIAL INFARCTIONS IN VARIOUS COMMUNITIES IN ISRAEL

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RESEARCH into the nature of coronary atherosclerosis and of atherosclerosis in general has provided important data concerning the anatomic, experimental, biochemical, genetic, and constitutional aspects of the disease. It should be expected that data comparing the incidence of coronary atherosclerosis in various population groups might provide useful information as to one of the main problems of the genesis of human atherosclerosis: the relative importance of exogenous and intrinsic factors.

Whereas a good deal of information is available on the over-all incidence of coronary artery disease in several countries, mostly in the form of death certificate statistics or of reports such as the painstaking studies of Morris[1] or Ryle and Russell[2] in England and Wales, exact information on the comparative incidence of the disease in various social strata and communities or populations is comparatively scarce. Much of the work presented, apart from the understandable interest of the medical profession in the ravages of coronary sclerosis in its own ranks, represents impressions rather than figures. Most textbooks devote at best a few lines to the ethnographic aspect of atherosclerosis and of coronary artery disease. Some of the information available is summarized in recent reviews, such as those of Bruger and Oppenheim[3] and Kellner.[4] White[5] stresses the need for further studies of the anthropological and hereditary aspects of the disease. Blache and Handler[6] recently noted ". . . that the rate at which aging processes develop in the coronary arteries in Negroes lags behind that in white individuals." They point out that in Negroes there is ". . . less disease of the coronary arteries and a lower autopsy incidence of coronary thrombosis." Pennell and Lehmann[7] found a larger proportion of heart disease deaths accounted for by diseases of the coronary arteries among white persons when comparing the mortality from heart disease in Negroes and white persons. De Langen[8] gained the impression that, anatomically, coronary sclerosis was about evenly distributed among the Javanese, Chinese, and European population of Indonesia although there were great differences as to the clinical symptomatology.

In the Japanese,[9] Eskimos,[9] the Chinese in China,[10] Costa Ricans,[11] and Okinawans,[12] atherosclerosis has been described as rare. This fact has usually been related to their low cholesterol intake. Ismail[13] has made similar observations for the native population of Egypt in its lower social classes. Hyman,[14] on

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the other hand, found coronary disease to be common among Melanesians, but interestingly enough, only rarely accompanied by anginal pain.

A survey of these reports as well as clinical experience teaches that the incidence of coronary atherosclerosis is studied best by pathologic data. Since this can only rarely be achieved on a large scale, the next best indicator would be the incidence of myocardial infarction. Although the proportion of myocardial infarctions to coronary atherosclerosis in general may vary among different groups, the number of myocardial infarctions will certainly be a more reliable source of information than the number of patients suffering from anginal attacks or data to be gained by electrocardiographic mass screening.

The present inquiry into the incidence of myocardial infarction within the various communities in this country was stimulated by our clinical impression that myocardial infarctions were occurring at an unequal rate in the various groups of the population of Israel, a country comprising today a great variety of both settled and newly immigrated Jewish people, and also of Arabs and other elements.

The great majority of the Jews here as elsewhere belong to three main groups: Jews originating from East, Central, and West Europe, called Ashkenazi Jews; secondly, Jews derived from Spain and some other Mediterranean countries, called Sefardi Jews; and thirdly, Jews originating from the countries around the Eastern Mediterranean (the Arab countries, Kurdistan, Iran, etc.), called Oriental Jews. Certain differences, to be briefly outlined later, prevail among these groups.

METHOD AND MATERIAL

The cases of myocardial infarction hospitalized by several medical services of this country were reviewed and tabulated according to the communities to which the patients belong. A number of instances of myocardial infarction (coroner's cases or cases being brought from other institutions for autopsy) found upon post-mortem examination at the Pathological Institute of our hospital are included. The cases of myocardial infarction autopsied after having been patients in the wards of this institution, however, are included in the clinical series of figures of Table III.

A few remarks as to the relative part of each community within the total population ought to be made here. These proportions have been in a state of flux because of a continuous large flow of immigration within the last few years, overwhelmingly from oriental countries. Altogether, the relative figures for the three main groups in the whole country in 1943*, 1949, and 1951, respectively, are presented in Table I. Every hospital service serves a different area, and there the proportion might be somewhat different.

Hospital I serves the city of Jerusalem mainly, in which Oriental Jews represent about one-third of the Jewish population, as well as a large adjacent area settled largely by Oriental Jews. Table II gives the admission figures pertaining to the medical departments of this institution for the years 1942, 1949, 1951 as an example, broken up as to members of the various communities.

*Figures for 1941 and 1942 not available.

TABLE I. DISTRIBUTION OF COMMUNITIES WITHIN THE JEWISH POPULATION IN ISRAEL*

YEAR	1943 (%)	1949 (%)	JUNE, 1951 (%)
Ashkenazi Jews	79.4	69.5	52.3
Sefardi Jews	8.8	13.5	11.5
Oriental Jews			
Yemenite Jews	4.7	7.3	6.4
Other Oriental Jewish Communities	7.1	9.7	19.8

*Figures obtained by courtesy of Dr. G. Kallner, Central Bureau of Statistics, Government of Israel.

Hospital II serves a city community as well as a number of major immigrant camps and the proportion of Oriental Jews is certainly not below the country's average. The number of admissions of members of the Oriental Jewish community was about 20 to 30 per cent in 1951.

TABLE II. ADMISSIONS TO THE MEDICAL WARDS OF THE HADASSAH UNIVERSITY HOSPITAL, JERUSALEM IN 1942, 1949, AND 1951, ACCORDING TO COMMUNITIES

YEAR	1942	1949	1951
Ashkenazi Jews	829	556	653
Sefardi Jews	100	108	124
Oriental Jews	180	156	221
Others	44	8	2
Total	1153	828	1000

Hospitals III, IV, and V provide service for smaller towns, large rural areas, and immigrant camps. Everywhere the admission rate of Oriental Jews is about 20 per cent or more, and especially at Hospital IV a great number of Yemenites were admitted during a large part of the period covered here. Hospital V takes care of a particularly young immigrant population, probably with a larger percentage of Oriental Jews than elsewhere in the country, and has a fifteen-bed medical service, which is the only one in a large area.

RESULTS

Table III reviews the cases of myocardial infarction collected in the respective institutions for the periods examined. The small number of cases belonging to the Oriental Jewish communities is evident. The prevalence of this disease among Ashkenazi Jews seems to be clearly borne out, especially for the Jerusalem community for which the largest figures are available (Hospital I) but the same trend is obvious for the other Medical Services reviewed except Hospital V where the total figure is very small.

DISCUSSION

Whereas Oriental Jews represent about 26 per cent of the whole population of this country, and at its lowest during the years reviewed represented 12 per

TABLE III. MYOCARDIAL INFARCTIONS HOSPITALIZED, ACCORDING TO THE VARIOUS COMMUNITIES IN ISRAEL

HOSPITAL	PERIOD OF OBSERVATION	NO. OF MYOCARDIAL INFARCTIONS	ASHKENAZI	SEFARDI	ORIENTAL	CHRISTIAN	NEGRO	UNDETERMINED
I. Rothschild Hadassah University Hospital, Jerusalem	Jan., 1941 to Aug., 1952							
a. Medicine		197	169	13	13	2		
b. Pathology		24	17	3	1	1		2
Total		221	186	16	14	3		2
II. Rambam Government Hospital, Haifa	June, 1951 to Aug., 1951	83	77 distribution unknown		5		1	
III. Government Hospital, B'nei Brak	March, 1950 to Aug., 1951	66	63	3				
IV. Assaf Harofe Gov't. Hospital, Zrifin	Sept., 1949 to June, 1952	40	30	7	2	1		
V. Hadassah Memorial Hospital, Beersheba	July, 1950 to June, 1952	2	1		1			
Total		412	280	26	22*	4	1	2
			(excluding hospital II) Total including hospital II = 383					

*= 5.3 per cent of total of myocardial infarctions.

cent (1943), their part in this group of cases of myocardial infarctions is only 5.3 per cent. For Hospital I the admission rate of this group was 15 per cent in 1942 and 22 per cent in 1952, whereas their percentage among the myocardial infarction group in the same years was only 6.3 per cent. These figures point to a statistically significant difference. The same holds true for the large share of the Ashkenazi community (about 85 per cent of myocardial infarctions).

Basing her figures on death certificate statistics, Kallner[15] recently concluded that in the group of arteriosclerotic heart disease there is a very marked preponderance for individuals of Occidental origin—16.5 per cent of adult deaths as compared with 4.6 per cent in Orientals.

We feel that no further statistically valid conclusions could be drawn from figures collected from a population which is in a continuous state of change as to its ethnic composition. The argument as to the difference in life expectancy of the various communities, however, could not be fairly employed to invalidate our conclusion: the higher mortality of the Oriental groups is mainly one of infancy and a large number of cases from the Oriental communities who are admitted to the hospital services have reached the age where severe coronary disease might occur.

The complete absence of cases in Arabs from this series, although Arabs represent about 9 to 10 per cent of the country's population (1952) does not per se prove the rarity of this condition among this part of the population. The hospitals from which the material for this study has been compiled are not in close proximity to the prevalently Arab settled regions of the country, especially not to its urban parts.

Differences in the distribution of coronary atherosclerosis among various ethnic groups as the ones mentioned in our introduction have been adduced as proof for the exclusive or prominent role certain extrinic or intrinsic factors may play in the causation of atherosclerosis in general and of the coronary vessels in particular. This way of reasoning, however, seems to us hardly permissible. As to the particular fact we are dealing with—the comparative rarity of this disease in the Oriental group—the differences between these Jews and mainly the Ashkenazi Jews prevail on so many levels that any conclusion, for instance as to a genetic difference on the one hand or a difference in cholesterol intake on the other, would be highly conjectural.

These groups differ from each other, although in an overlapping fashion, at least on the genetic, constitutional, metabolic, psychological, sociological, and nutritional planes.

In their masses the Oriental Jews belong to the lower social classes and lead a more primitive way of life. Their tendency to become affected by certain diseases, among them so-called psychosomatic disorders, seems to vary from the other groups. Besides, they have been exposed to widely different climatologic and cultural conditions. Oriental Jews in general do not use less tobacco than others; obesity and diabetes seem to be rarer among them. Their dietary habits, until recently, have been different from those of the majority of Ashkenazi and many Sefardi Jews, but their cholesterol intake on the whole has not been less

than that of the latter. Hypertension seems to be much rarer among the Oriental group, but here exact figures are still lacking. No comparative anthropological and biochemical data in Oriental Jews are as yet available to discuss our findings from those points of view.

Yemenite Jews are of comparatively low stature, and, on the whole, of slender body build, but these physical characteristics are by no means a distinctive feature between the entire group of Oriental Jews and the other Jewish groups.

It should be pointed out here that the few Oriental Jews found ill with coronary disease have usually lived in this country for a considerable part of their lives. The only two incidences of myocardial infarction in Yemenite Jews, for example, have occurred after a stay of thirty-five and twenty-one years, respectively, in this country. Whether this has anything to do with Western ways of life customary in this country in contrast to the countries of their origin, only the future will teach.

The problem of etiology of coronary atherosclerosis most probably does not lend itself to a single factor solution. A complex interrelationship among genetic, biochemical, and anatomical factors on the one hand and psychological and social stress, nutrition and other external factors on the other, with varying emphasis on one or the other has to be assumed. New data, such as those presented here, will have to be related to this complex situation.

SUMMARY

Data on the ethnic distribution of coronary atherosclerosis are comparatively scarce. Stimulated by the impression that coronary artery disease affected the various Jewish communities of Israel unevenly, a series of cases of myocardial infarction was reviewed as to the incidence of this disease within these various groups. The analysis of 412 cases of myocardial infarction showed that the incidence in Ashkenazi Jews was disproportionately high, whereas Oriental Jews showed an incidence rate of 5.3 per cent only, although today they constitute at least 26 per cent of the country's population and were never less than 12 per cent during the period reviewed. This difference in the occurrence rate and some of its implications are discussed.

The author is greatly indebted to the following physicians who provided him with the figures of their respective medical departments: Dr. W. Alkan (Assaf Harofe Government Hospital, Zrifin), Dr. P. Efrati (Government Hospital, B'nei Brak), Dr. J. Heichman (Rambam Government Hospital, Haifa), Dr. E. Lehmann (Hadassah Yassky Memorial Hospital, Beersheba).

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STUDIES ON SPONTANEOUS VARIATIONS IN BLOOD COAGULABILITY IMMEDIATELY FOLLOWING MYOCARDIAL INFARCTION

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NEARLY TEN years have elapsed since the introduction of the treatment of myocardial infarction by anticoagulant therapy.[1,2,3] Opinion with regard to the application of such treatment remains divided. Nevertheless, a large amount of research done on the subject would appear to indicate that the anticoagulants do improve the prognosis in infarction, reducing both the over-all mortality and the incidence of thrombo-embolic complications.[4-10]

However, the decision to use anticoagulants for a particular infarct seems to be based too frequently upon ill-defined criteria. Certain authors pay particular attention to such factors as the apparent seriousness of the attack, the degree of peripheral failure, the extent of the lesion (as indicated by the electrocardiogram), the age of the patient, or the presence of an early thrombo-embolic complication. Others recommend treatment only for patients who have sustained an infarct previously. The majority of workers, on the other hand, give treatment routinely without discrimination whenever the diagnosis of infarction is made and whatever the stage of its evolution.

The duration of treatment is equally arbitrary. Frequently, the decision to give treatment for one month is made a priori without any good reason and with the general appearance of the patient serving as the only guide.

In our opinion there can be no doubt that it is this vagueness which surrounds the indications, methods of surveillance, and optimum duration of the treatment which largely accounts for divergences of opinion over its dangers, achievements, and usefulness.[11] For this reason it appeared to us important to make a study of the coagulability of the blood in a series of untreated cases of myocardial infarction throughout their entire course from the onset of the first severe attack of pain right up to functional recovery in order to discover whether there were any significant, spontaneous fluctuations in coagulability occurring in the absence of any form of anticoagulant treatment. At the same time, an attempt was made to delineate the indications which should guide the choice of appropriate occasions when anticoagulant therapy is most likely to succeed.

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CLINICAL MATERIAL

The material studied consisted of seventy cases of recent myocardial infarction collected over a period of two years, all supported by a classical history together with typical electrocardiographic changes of muscle necrosis, injury, and ischemia taken at various stages in the evolution of the disease. In six cases there was post-mortem control.

The initial measurements of blood coagulability were made: within twenty-four hours of the attack in twelve cases; within forty-eight hours of the attack in thirteen cases; within four days of the attack in thirty-two cases; and between the fourth and ninth days in thirteen cases. In other words the first blood test was always made within ten days of the attack, further tests being made every two days at first and then later at more widely spaced intervals. In all, 282 blood examinations were made for these seventy patients. The results have been classified and analyzed in terms of the time of onset of the attack of pain for each case considered. Where patients were treated, the results from the period after the institution of treatment have not been included in the present study.

TECHNIQUES

Measurement of coagulability has consisted of the following three routine investigations: 1. heparin tolerance test (in vitro); 2. plasma prothrombin; 3. plasma fibrinogen.

1. *Heparin Test* (heparin tolerance test in vitro).—This estimation is made on the oxalated plasma of venous blood using a modification of the technique of Soulier and Le Bolloch.[12,13] Blood is taken in the morning by venipuncture, a light tourniquet being left in place while 11 or 12 c.c. of blood are rapidly aspirated into a completely dry syringe using one prick with a needle 1.2 mm. in diameter. Ten cubic centimeters are immediately transferred to a bottle containing 1 c.c. of dried Wintrobe solution (potassium oxalate 0.8 Gm.; ammonium oxalate 0.12 Gm.; distilled water to 100 c.c.). The whole procedure should be completed in less than one minute.

The reagents used are: (1) patient's oxalated plasma, separated by centrifugation at 1,800 revolutions per minute for five minutes, kept in a cool place, and examined within six hours of its collection; (2) a solution of calcium chloride, 3 Gm. per liter (Solution I); (3) a commercial preparation of heparin (Héparine Vitrum containing 50 mg. per cubic centimeter); this serves as a stock solution. From the stock solution three working solutions of heparin are obtained by dilution with the calcium chloride solution (Solution I) as follows: (a) Solution II—6 gammas heparin per cubic centimeter. (b) Solution III—10 gammas heparin per cubic centimeter. (c) Solution IV—13 gammas heparin per cubic centimeter.

These solutions are to be used at 37.5°C. but may be kept in a cool place for over a week. If the reactions are carried out at temperatures below 37°C. weaker solutions of heparin would be required; thus at 35°C. the results usually given for Solution IV would be obtainable using a concentration of 11 gammas per cubic centimeter.

The test is carried out in a bath at 37.5°C. using a series of identical ordinary glass tubes (80 by 12 mm.). Four tubes, containing respectively 0.5 c.c. of one of the Solutions I, II, III, IV, are placed in the water bath for five minutes and left until a constant temperature is reached Plasma (0.5 c.c.) is then added to each tube, the tubes are shaken to ensure adequate mixing, and a stop watch is started. (Six tests can be carried out at one time, each series of four tubes being filled at one-half minute intervals.)

Coagulation is observed at first by gentle tilting of the tubes every thirty seconds, then, as the end point is reached, by completely inverting them, starting with tube I which gives the shortest time and concluding with tube IV. This corresponds to the time measured by Howell's method. The time which has been of greatest value in our work is that measured in the last tube (IV); this gives the time required for complete coagulation. All these precautions ensure

maximal accuracy in the reading of results, particularly if the investigations are conducted by the same technician and provided that a control specimen of plasma is invariably included in each series of tests. Consistent and reliable results can be obtained only by strict adherence to these conditions. In this article the only figures given are those of the coagulation time in tube IV where there is the greatest concentration of heparin. Among 115 control subjects examined between July, 1950 and July, 1951, and chosen from among the medical and nursing staff of the Hôpital Boucicaut the following results were recorded for tube IV (354 tests):

mean time : 11.2 minutes
standard deviation : ± 1.56 minutes
deviations from the mean : + 5.3 minutes / − 2.7 minutes

Menstruating women, subjects over 60 years of age, people convalescent from any disease whatever, and those who had recently suffered trauma or undergone surgical operation were not accepted as controls for this series.

The consistency of the above results of these tests applied to normal persons justifies the use of the method in a comparative study of abnormal individuals. Variations from the normal may be considered to constitute a true increase or decrease of coagulability only when the times for the heparin test are more than three minutes shorter or longer than the average time for the control group. For convenience the plasma may be spoken of as hyper- or hypocoagulable according to whether the heparin tolerance is increased or decreased in comparison with the control. It is noteworthy that bed rest appeared to make no measurable difference in the results of the heparin test.

2. *Plasma Prothrombin.*—The prothrombin time (that is the "activity" of prothrombin) was most frequently measured by the Quick method,[14] but in some instances use was made of the 12.5 per cent plasma prothrombin time of Link and Shapiro[15] for which the plasma is diluted to 12.5 per cent with isotonic saline. The results are expressed as the prothrombin time and also as the percentage of prothrombin concentration compared with the normal. It is known that these techniques make no allowance for the influence upon prothrombin of factor V (Ac-globulin or labile factor) or of factor VII (convertin, SPCA). Furthermore, the Quick method is not sensitive to the effects of heparin or heparin-like substances subsequently appearing in the plasma. As a supplementary investigation, the concentration of labile factor has sometimes been investigated by Stefanini's method.[16]

3. *Plasma Fibrinogen.*—This was calculated by weighing the fibrin obtained after coagulation by thrombin and desiccation for twenty-four hours at 37° Centigrade.

RESULTS

1. *Heparin Test.* (Figs. 1 and 2, Table I).

(*a*) The test has shown that in the first twenty-four to forty-eight hours following myocardial infarction the coagulation time is very short; there is a hypercoagulability of the blood. This was observed in every case which could be examined during the initial period (twelve cases during their first twenty-four hours). The degree of such hypercoagulability is maximal in the first few hours, thereafter diminishing. Two subjects examined within six hours had times of 4.5 minutes and 5.5 minutes respectively. It has been demonstrated that this initial hypercoagulability is a constant phenomenon accompanying the occurrence of the infarct. Indeed it is probably the continuation of the hypercoagulability which we have observed with great regularity (twenty-four times out of twenty-six) in another series of cases in the state of "impending infarction."[32]

(b) From the second to the eighth or tenth day the test very frequently shows hypocoagulability of a varying degree which reaches its maximum between the second and fifth days, on an average about the third day. This can become

TABLE I.

Days after infarction		First 24 hr.	2	3	4	5 to 6	7 to 8	9 to 10	11 to 12	13 to 14	15 to 16	17 to 18	19 to 21	22 to 27	28 to 35	36 to 43
Number of cases		12	16	25	22	35	38	28	19	11	14	12	12	13	14	11
Mean coagulation time in minutes for heparin solution IV		6.4	10.9	15.4	17.1	15.1	11.5	11	8.6	8.1	6.5	7.2	6.7	7.3	8.3	9.7
Deviations from the mean	+	1.6	8.1	12.6	8.9	14.9	8.5	6	7.4	3.9	4.5	3.8	2.8	3.7	3.7	3.5
	−	1.9	6.4	10.9	8.1	8.6	7	5.5	6.1	3.1	4.5	2.7	1.7	2.8	2.3	7.7
Standard deviations $\sigma = \sqrt{\frac{\Sigma d^2}{n}}$	±	1	3.5	4.7	4.7	4.8	3.7	3.3	3.4	2.5	2.3	1.9	1.4	1.8	2.2	3

extreme, for the coagulation time may be more than twice that of the control. This state usually lasts for about one week, gradually passing back to the normal condition of isocoagulability, though often taking as long as two weeks to do so.

This phase of secondary hypocoagulability is seen frequently but not invariably. It was present fifty-seven times among the seventy patients (81.4%). It failed to appear on thirteen occasions (18.5%), in eight of which the initial hypercoagulability was persistent while in the other five coagulability was within normal limits. The theoretical and practical importance of this phase of spontaneous hypocoagulability between the second and tenth days after the majority of infarcts is paramount, as will be seen later.

(c) Between the fifth and fifteenth days, usually at about the eighth day of the disease, the heparin test shows hypercoagulability of varying intensity, often

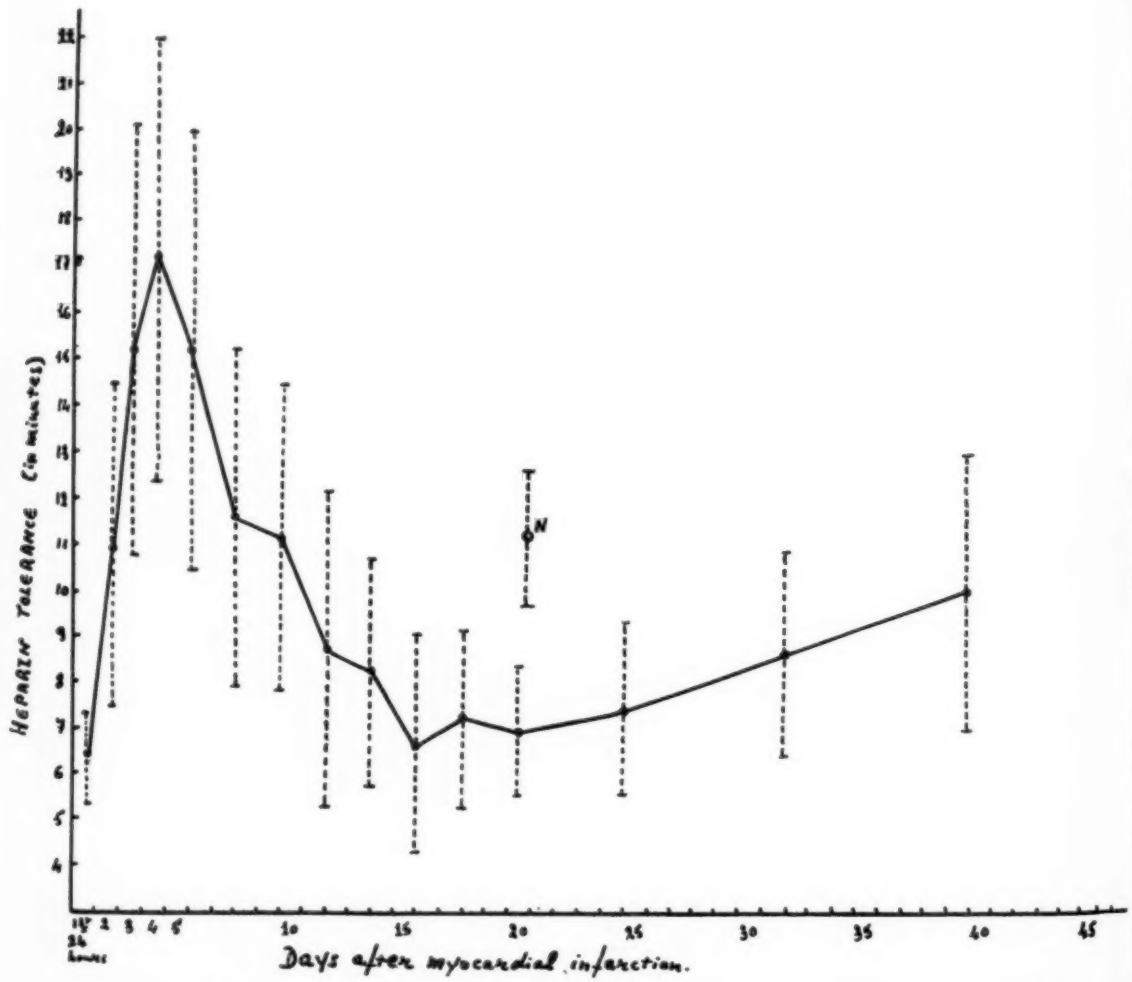

Fig. 1.—Changes in the findings of the heparin test (in vitro) in seventy cases of recent myocardial infarction: Mean values and Standard Deviation. N = mean value and Standard Deviation for 115 normal controls.

very pronounced. Sometimes coagulation may occur in as short a time as five or six minutes, or one-half the control coagulation time. Indeed in two cases the time was reduced to two minutes and did not seem to be prolonged at all by heparin in any concentration used (up to 13 gammas heparin per c.c.). Not only the degree but also the duration of this hypercoagulability is extremely variable; it may last from a few days to several months, but in general it extends for three or four weeks.

The heparin test reveals beyond any doubt a definite and characteristic march of spontaneous variations in coagulation time following untreated myocardial infarction passing through three phases:

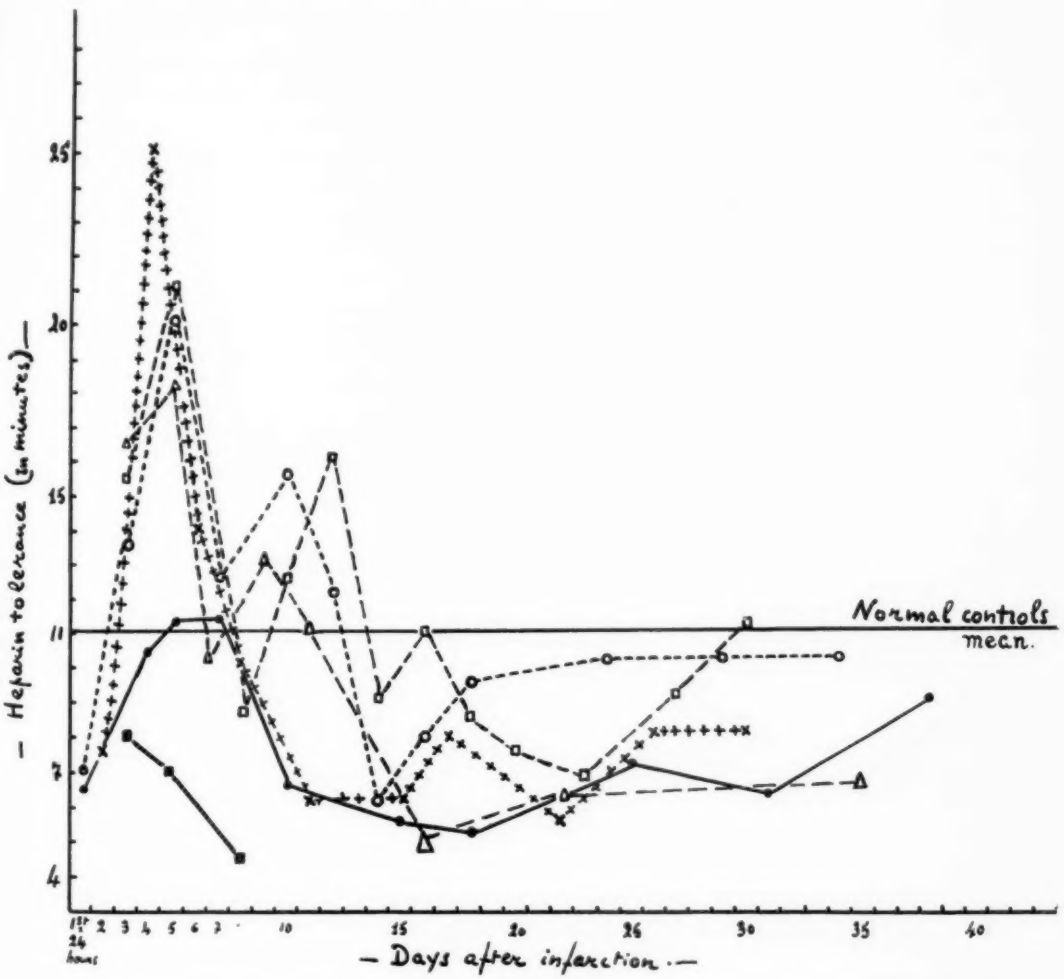

Fig. 2.—Changes in the findings of the heparin test (in vitro) in six cases of myocardial infarction.

× + + + ×
□——□
○——○
△——△ } Four cases showing a frank secondary hypocoagulability.

●——● One case showing it to a lesser degree.

■——■ One case where hypercoagulability occurs during the same period.

First phase. The period of initial extreme hypercoagulability; this is constant and of brief duration and occupies the twenty-four to forty-eight hours which follow the beginning of the attack.

Second phase. The period of spontaneous secondary hypocoagulability; this lasts about seven days and occurred in 81.4 per cent of cases in this series.

Third phase. The period of late hypercoagulability; this is variable in degree though constant in occurrence and often greatly prolonged.

2. *Plasma Prothrombin.*—The whole plasma prothrombin time, the 12.5 per cent plasma prothrombin time, and the concentration of labile factor showed various modifications following the infarct.

Within twenty-four hours of the attack there was no recognizable change. Between the second and the eighth or tenth day (period of spontaneous secondary hypocoagulability according to the heparin test) a definite prolongation of the whole plasma prothrombin (Quick) time (from 1 to 4 seconds) was constantly observed, whereas the 12.5 per cent plasma prothrombin (Link-Shapiro) time became slightly shorter or remained normal. The concentration of labile factor (studied in eight patients only) stayed within normal limits in six and was considerably increased in the other two patients.

Beyond the eighth or tenth day (late hypercoagulability stage) the Quick time often continued to be prolonged even though the Link-Shapiro time and the concentration of labile factor kept within normal limits.

3. *Plasma Fibrinogen* (in collaboration with R. Bourgain).—Within twenty-four to forty-eight hours following infarction the plasma fibrinogen level did not transgress normal limits (six cases studied). At the end of the first twenty-four or forty-eight hours the level rose quickly and constantly to a peak occurring between the third and sixth days. In twelve of twenty-two cases the plasma fibrinogen exceeded 1.0 Gm. per 100 cubic centimeters (in one, reaching 1.4 Gm. per 100 c.c.).

Thereafter, beyond the seventh day, the level fell slowly to reach the normal within one or two months.

It is worthy of mention that in the twenty-two cases studied maximal fibrinogen levels were reached within the hypocoagulability period.

DISCUSSION

The heparin test of Waugh and Ruddick[17] as modified by Soulier and Le Bolloch[12] gives an over-all idea of the blood's tendency to coagulate.

In general, this test provides results comparable with those obtained by Howell's technique or by measurements of whole blood coagulation time, but it furnishes a more precise notion of coagulability. The similarity between this test and that of De Takats[18] (heparin tolerance in vivo) is not striking, for the results of the latter are vitiated by chemical changes which injected heparin undergoes in the course of metabolism. The concept of coagulability given by

the heparin test[12,19,20] is so faithfully imparted that one may translate its results by the terms hyper- and hypocoagulability.*

Applied to the study of myocardial infarction the test shows that the three phases outlined above follow in strict order: initial hypercoagulability; secondary, spontaneous hypocoagulability; and late hypercoagulability. Ogura and Fetter[21] and, more recently, Rosenthal and Weaver[22] have described the state of hypercoagulability following myocardial infarction, but their findings apply to what we have described as the third phase and they make no mention of the first two phases.

The state of hypercoagulability is believed to play a leading rôle first in the causation of coronary thrombosis and secondly in the liability to thromboembolic complications, the remarkable frequency of which has been re-emphasized in a recent anatomic study.[23] In addition there is much supporting evidence for such a hypothesis but no attempt is made to summarize it in this article.

Hypercoagulability is a poorly understood biologic phenomenon occurring in many circumstances[24] such as infections, trauma, post operative states,[25] excessive diuresis following the mercurial compounds,[26,27] overwork, and even emotional change.[28]

The fundamental causes of hypercoagulability remain completely obscure. The Quick test never shows an increase in the amount of prothrombin, while the plasma fibrinogen is actually at its highest during the period of hypocoagulability. This suggests that the basic cause of the hypercoagulability is an enzyme operating at the initial stage of coagulation.

The secondary, spontaneous hypocoagulability which we have demonstrated in 80 per cent of the myocardial infarcts studied between the second and eighth day of the disease does not belong solely to coronary thrombosis. We have found it to exist after pulmonary and cerebral embolism and, to a lesser degree, after embolism of the limb arteries.[29] Ogura and Fetter[21] and Rosenthal and Weaver[22] attach no importance to hypocoagulability following coronary thrombosis, but Schilling and De Natae[30] draw attention to the rapid appearance of auto-anticoagulants after coronary thrombosis and pulmonary thrombosis and embolism. The mechanism and underlying origin of this curious, transitory, spontaneous hypocoagulability have not been elucidated. In all probability the changes which take place are due not to the actual occlusion of the artery but to the liberation of some unknown substance originating from the necrotic myocardium. This hypothesis would explain the delayed appearance of the hypocoagulability. (It becomes established only on the third day.) The invariable return of an appreciable degree of hypercoagulability about the eighth to tenth day after the infarct is due to the reappearance of the essential biologic dyscrasia which originally paved the way for the thrombosis. The chain of events leads one to suppose that after some days the necrotic myocardium exhausts its faculty to

*The heparin test shows a prolonged time in thrombocytopenia, hemophilia, hypoprothrombinemia, fibrinopenia (less than 0.1 Gm. per 100 c.c.), and in hemorrhagic diathesis due to the presence of an auto-anticoagulant. The time is foreshortened in the presence of excess of any substance accelerating coagulation (thromboplastin-like enzymes and substances promoting the conversion of prothrombin to thrombin) also, theoretically, by deficiency of heparin cofactor.[12]

produce the hypocoagulant substance, so that, in consequence, the underlying fundamental process, whatever it be, gives rise to delayed thrombo-embolic complications.

The recognition of the three stages in the evolution of coagulability following untreated myocardial infarction has provided valuable information upon which to base a rational system of treatment with heparin and a brand of ethyl biscoumacetate.*

The knowledge of the existence of spontaneous hypocoagulability makes it clear that anticoagulant therapy is contraindicated between the second and eighth or tenth days. Such treatment would carry the risk of provoking hemorrhages particularly in the organizing area of necrosis and in the adjacent pericardium. The further knowledge that, under pathologic conditions, there is little correlation between the heparin test and the plasma prothrombin level demands that treatment should not be preoccupied with a meticulous control of the prothrombin concentration at a figure between 10 per cent and 30 per cent but rather directed to the maintenance of a true hypocoagulability regardless of any type of prothrombin estimation.

We therefore feel that a too rigid policy towards anticoagulant treatment is dangerous. All questions of institution, maintenance, and suppression of drugs should be settled only according to the time at which the patient is seen and the laboratory findings.

Immediately after the infarct, prompt recourse to heparin should be taken and the drug continued for twenty-four to thirty-six hours. Where the patient is seen on or after the second day, no anticoagulants should be given unless there is evidence of a persistent hypercoagulability. The Quick test and the heparin test are carried out simultaneously each day and treatment withheld until they disclose that the patient has reached the period of late hypercoagulability. The patient seen later on, after the eighth day, has in all probability passed into the third phase. Nevertheless, treatment may be instituted and controlled only with the regular guidance of the two tests. The ultimate cessation of treatment is justifiable only when the results of both tests clearly indicate the end of the tendency to hypercoagulability.†

Using a systematic application of the two laboratory tests we have obtained good results with a minimum of untoward reactions in a series of seventy-one cases[31] of acute myocardial infarction treated with anticoagulants (heparin and ethyl biscoumacetate).

In all, seven patients (9.8 per cent) died during the first two months of treatment. Thrombo-embolic complications during treatment were very rare, occur-

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*3,3′—carboxymethylene bis (4-hydroxycoumarinyl) ethyl ester or Tromexan.

†By tendency to hypercoagulability is meant a state of disproportion between the two tests, the heparin test failing to show as profound a hypocoagulability as would otherwise exist for a given prolongation of the prothrombin time, for example, a patient with a heparin tolerance time equal to that of the control and a prothrombin concentration of 15 per cent. In the patient who does not show the tendency, a frank hypocoagulability is obtained when treatment with coumarin substances has reduced the prothrombin concentration to 30 per cent. (Fig. 3.)

ring in two cases only (2.8 per cent), one fatal pulmonary embolism on the eighth day in a patient still showing signs of hypercoagulability and one transient hemiplegia twenty-four hours after the initiation of treatment. These results may be evaluated by comparing them with those of a series of ninety-six cases of myocardial infarction treated in the same hospital service without anticoagulant therapy between January, 1947 and January, 1950. The results were as follows: Over-all mortality in the first two months, thirty-six cases (37.4 per cent); thrombo-embolic complications, forty cases (41 per cent) including twenty-two deaths (22.8 per cent) with post-mortem control in nineteen cases.

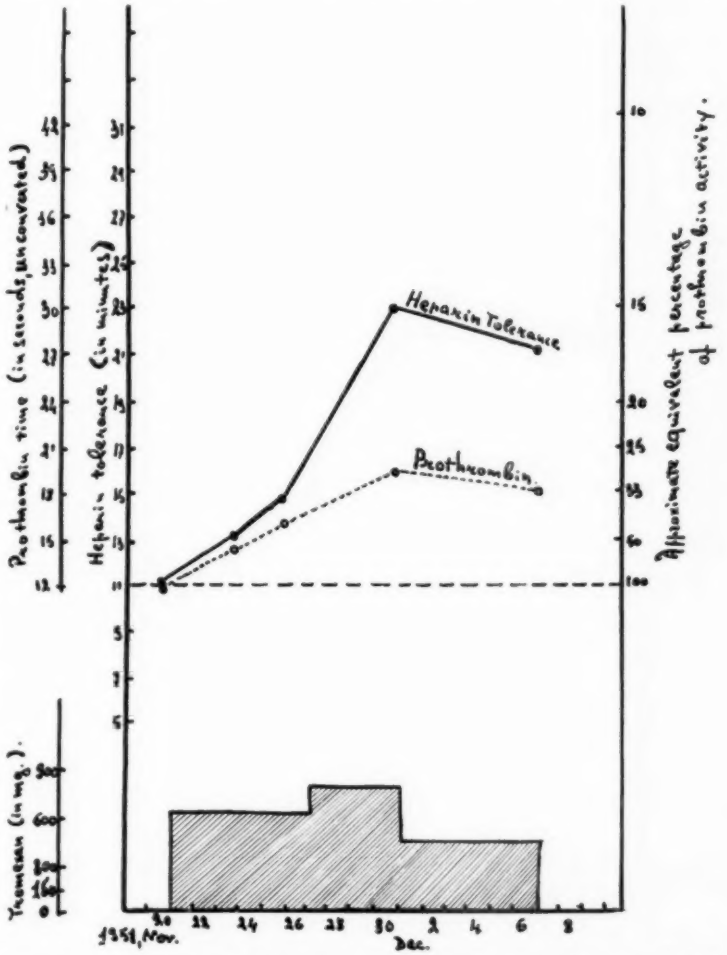

Fig. 3.—Changes in the findings of the heparin test (in vitro) and the plasma prothrombin in a normal subject taking ethyl biscoumacetate tromexan. Frank hypocoagulability is obtained when the prothrombin concentration is less than 30 per cent.

The incidence of untoward bleeding during treatment was considerably less in our series than has been observed by other workers. It was never serious and occurred in nine cases altogether (12 per cent) including five cases of hematuria (two frank, three microscopic), two cases of hematoma of the buttock after intra-

muscular penicillin, and two cases where hemopericardium probably occurred forty-eight and seventy-two hours respectively after the institution of intensive anticoagulant treatment mistakenly prescribed during the phase of spontaneous hypocoagulability (both patients recovered). (Fig. 4.)

We feel that the small incidence of hemorrhagic complications speaks highly for the accuracy of the method of control which was used[33] for it permits an extremely fine adjustment of the dosage of anticoagulant (tromexan) to the exact requirements of the patient. The three advantages of this type of control are: (1) Treatment is not given during the period of spontaneous hypocoagulability. (2) Overdosage is prevented. (3) It ensures that adequate therapy is given to overcome a stubborn spontaneous hypercoagulability even if this entails persisting with therapy after the prothrombin concentration has already passed below 10 per cent.

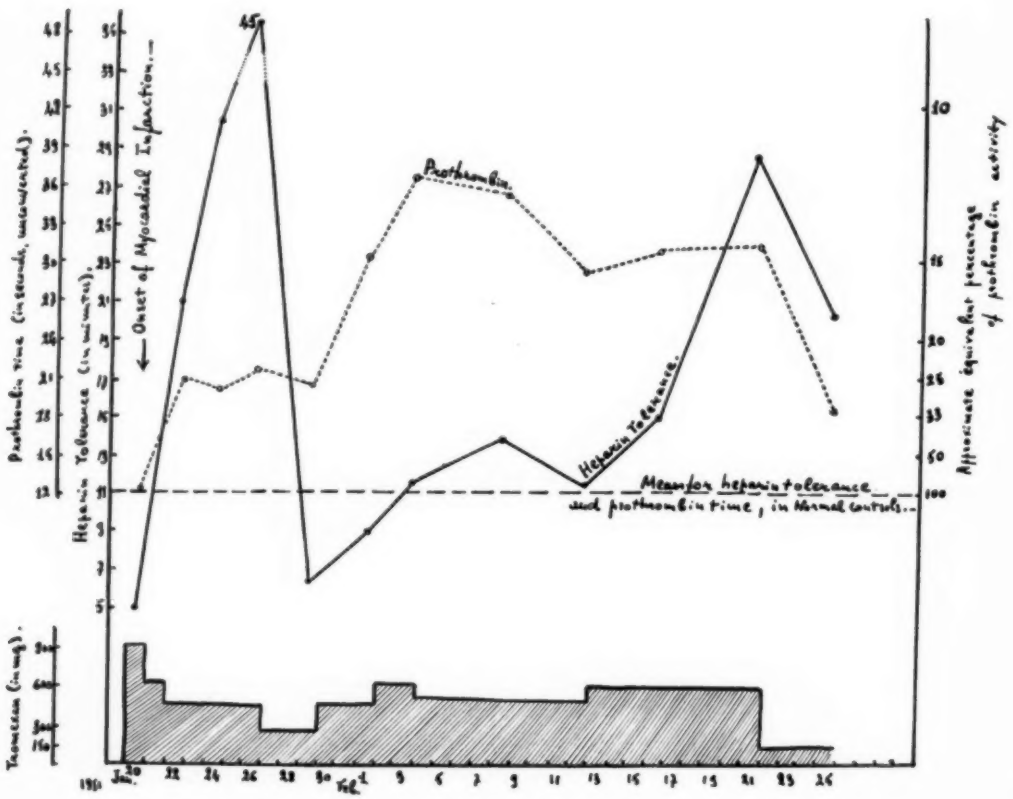

Fig. 4.—Changes in the findings of the heparin test (in vitro) and the plasma prothrombin in a case of myocardial infarction treated with tromexan. This figure demonstrates the disproportion between the plasma prothrombin and coagulability as indicated by the heparin test at various periods during the time following the acute attack; between Jan. 21 and 27 (second to eighth day after the infarct) there is summation of the two hypocoagulant influences (spontaneous and therapeutic); between January 28 and February 20 there is a disproportion between the two curves indicating the existence of the tendency to hypercoagulability; from February 21 onwards the normal correspondence between the two tests is restored.

SUMMARY

The evolution of spontaneous variations in the coagulability of the blood following myocardial infarction has been studied in seventy untreated cases by simultaneous estimations of the prothrombin time and the heparin tolerance test (in vitro).

1. Starting from the acute attack, three phases succeed one another with great regularity:

(a) Period of hypercoagulability, often extreme, occupying the first twenty-four to forty-eight hours. Very constant.

(b) Period of spontaneous, secondary hypocoagulability from second to third to eighth to fifteenth day, usually lasting about seven days. Occurred in 81.4 per cent of cases in the series.

(c) Period of late hypercoagulability, variable in degree, starting on about the eighth or tenth day and lasting usually a few weeks but possibly several months.

2. The demonstration of these spontaneous fluctuations of coagulability have enabled us to elaborate a rational system of anticoagulant treatment which has been applied to seventy-one cases of infarction with good results (over-all mortality: 9.8 per cent, thrombo-embolic complications: 2.8 per cent), and a small incidence of inconsequential bleeding (12 per cent).

3. Frequent studies of blood coagulability are essential to any treatment with coumarin substances. The prothrombin time by itself is not enough; measurements of the heparin tolerance in vitro must always be made at the same time.

We wish to thank Doctor D. K. Briggs of the American Hospital of Paris for the translation

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THE HEPARIN TREATMENT OF ANGINA PECTORIS

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THE use of heparin in the treatment of angina pectoris was reported in 1949 by Gilbert and Nalefski.[1] These authors suggested that the favorable results obtained might be attributed to an increased coronary blood flow. More recently Graham and associates[2a] reported marked symptomatic relief of angina pectoris with intravenous injections of heparin once or twice a week. Substitution of saline placebo injections for the heparin was followed by a return of anginal symptoms.

The purpose of this report is to describe our experience with the heparin treatment of angina pectoris.

MATERIAL AND METHOD

A large number of patients under treatment in the cardiac clinic for angina pectoris were screened. Only those with clear-cut angina and electrocardiographic changes, either at rest or after exercise, of the type usually associated with coronary disease (S-T and T changes) were accepted for study.

Of the thirteen patients selected there were twelve men and one woman, ranging in age from 58 to 75 years. Arteriosclerosis, hypertension, or both were present in all. In addition, five patients showed definite evidence of old myocardial infarction.

Each patient was treated for a period of forty weeks. Treatment consisted of alternating ten-week courses of intravenously administered heparin and of saline. In seven cases the initial course consisted of heparin. In the other six cases treatment was begun with saline.

Heparin was given in doses of 75 mg. (7.5 c.c.) twice weekly. Physiologic saline was administered in 7.5 c.c. doses twice weekly. Twelve-lead electrocardiograms were made before and at intervals during the study and included repeated exercise tests. The patient's usual medication was not altered, and the use of nitroglycerine was not interdicted. Each patient's response was judged on the basis of his own statement as to general well-being, the history of frequency and severity of anginal attacks, the amount of nitroglycerine used, the estimate of his walking tolerance, and also on observed electrocardiographic changes at rest and after exercise. Walking tolerance was the chief criterion.

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These data were arbitrarily graded using symbols of minus to indicate degrees of worsening, zero to indicate no change, and plus to indicate degrees of improvement.

RESULTS

Improvement in walking tolerance and anginal symptoms occurred in nine of the thirteen cases. This became evident during the early weeks of treatment and continued with some variations during the entire period of observation, regardless of whether heparin or saline was being administered (Table I). In the other four cases (No. 8, 10, 12, 13) there was no change in walking tolerance at any time during the period of observation. Twelve of the thirteen patients experienced an increased sense of well-being. Comparison of the control electrocardiograms with those taken at intervals during, and at the completion of, treatment failed to reveal any significant changes. No untoward effects of heparin were noted in any of the cases.

TABLE I. RESPONSE TO TREATMENT

CASE NO.	TYPE OF HEART DISEASE*	HEPARIN	SALINE	HEPARIN	SALINE
1	A.S.H.D. Old Myocardial Infarct	++++	----	+++	+++
2	A.S.H.D	++	+	++++	++++
3	A.S.H.D. Old Myocardial Infarct	+++	---	++	++
5	A.S.H.D.	+++	+++	++++	++++
6	A.S.H.D. Old Myocardial Infarct	++++	++	+++	+++
8	H.A.S.H.D. Old Myocardial Infarct	O	O	O	O
12	H.H.D.	O	O	O	O

CASE NO.	TYPE OF HEART DISEASE	SALINE	HEPARIN	SALINE	HEPARIN
4	H.A.S.H.D.	++	++++	++++	++++
7	L.H.D.	++	++	++	++
9	A.S.H.D.	++	++++	++++	++++
10	H.H.D.	O	O	O	O
11	A.S.H.D.	++	++++	++++	++++
13	A.S.H.D. Old Myocardial Infarct	O	O	O	O

*A.S.H.D.—Arteriosclerotic Heart Disease
H.A.S.H.D.—Hypertensive Arteriosclerotic Heart Disease
H.H.D.—Hypertensive Heart Disease
L.H.D.—Luetic Heart Disease
− = Degree of worsening
O = No change
+ = Degree of Improvement

DISCUSSION

Graham and associates[2b] reported marked relief of angina pectoris in patients who had received intravenous injections of 50 to 100 mg. of heparin once or twice a week. These investigators found that symptomatic relief was parallel to the shift in lipoprotein molecules from high to low S_f levels. Symptomatic relief occurred after the first few injections of heparin, whereas substitution of saline placebo for heparin injections was followed by return of anginal symptoms. Reference to our table reveals that similar effects were noted following the first

course of heparin and saline in Cases 1 and 3 and to a lesser degree in Cases 2 and 6. However, upon repetition of the procedures all these patients improved regardless of the material injected.

The striking feature in our series was the appearance of subjective improvement in walking tolerance in nine of the thirteen cases. The improvement began during the first week of treatment, regardless of whether therapy was initiated with heparin or with saline. In the four remaining cases in which there was no change in walking tolerance, this remained constant during treatment with both heparin and saline. In a recent report, Russek and associates[3] treated fourteen patients with short courses of heparin. They failed to note either subjective improvement or any electrocardiographic change in exercise tolerance. Our experience differs from that of Russek in that we noted improvement with heparin (as well as with saline). We are in agreement with their conclusions that heparin once or twice a week is of no value in treatment of angina pectoris.

Any discussion or investigation of angina pectoris should consider the emotional and personality structure of the individual. This investigation was conducted over a period of ten months with frequent interviews. An opportunity was thus afforded to observe these patients intimately with respect to their anginal state and for the patients to be impressed with the increased interest on the part of the doctors. There is no intention to imply that psychogenic factors alone operate in the production of angina pectoris. However, in our controlled series of thirteen cases in which we compared the effects of heparin with those of a placebo, subjective improvement was noted in twelve cases. In our judgment the improvement was due to the psychologic impact of a strikingly new form of treatment, and perhaps also to the beneficial effect of greater sympathy and manifested interest in the patient's welfare.

SUMMARY

1. Thirteen cases of angina pectoris were treated with alternating courses of intravenously administered heparin and saline. An increased sense of well-being was noted in twelve cases.

2. Increase in walking tolerance occurred in nine cases.

3. This subjective improvement occurred regardless of whether the patient was receiving heparin or saline.

4. In no case, however, was there any change in the electrocardiogram either at rest or after exercise.

5. It is concluded that heparin has no specific effect in angina pectoris when administered twice weekly.

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CARDIO-PERICARDIOPEXY FOR THE TREATMENT OF CORONARY ARTERY DISEASE

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IN 1905 Sherman[1] stated that the road to the heart is a straight line of two centimeters in length but it took 2,000 years to reach it. The value of surgery in the treatment of heart disease is now accepted, particularly in congenital anomalies and acquired mitral stenosis. Numerous surgical procedures have been attempted for the treatment of coronary artery disease but none has been widely accepted as yet. In this report we wish to present the beneficial results we have obtained with cardio-pericardiopexy and to advocate its more frequent application in the treatment of coronary disease.

In the past twenty-five years progress has been made in our knowledge of the pathologic anatomy and physiology of coronary sclerosis and coronary insufficiency. It is now accepted that the disability of coronary disease is due to functional or occlusive narrowing of the coronary arteries, which is manifested by anginal pain and results in myocardial ischemia, infarction, and necrosis. The natural progress of the coronary insufficiency may be slowed or prevented by the formation of an adequate collateral circulation.

In the early stages of coronary sclerosis the narrowing is usually confined to the larger coronary branches and the degree of occlusion tends to diminish from above downward. It is at this stage before the small arteries and arterioles are involved that a collateral circulation can be most effective. The collateral circulation may be intercoronary[2] through anastomotic vessels which join the left and right coronary arterial systems, or extracardiac[3] through anastomotic vessels joining the vascular bed of the myocardium with external vessels on the outer surface of the heart and in surrounding structures. Another factor pertaining to this process is that the smaller arteries and capillaries on the surface of the heart and the arteriae telae adiposae in the auriculoventricular groove become more prominent and increase in number with increasing age as the degree of coronary sclerosis progresses.[4] This serves as another source of intercoronary anastomosis. If occlusion of a large coronary artery takes place slowly, these two processes may produce a collateral circulation sufficient to prevent appreciable myocardial ischemia and infarction but in many individuals such compensatory processes are inadequate to prevent fatal coronary insufficiency.[2b]

The myocardium normally receives a small amount of collateral circulation from the pericardium through the internal mammary, bronchial and diaphrag-

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matic arteries.[1-3] Increased vascularity of the pericardium or adhesions between the myocardium and the mediastinal structures will increase this normal collateral circulation. This is clinically supported by the observation that patients with adhesive pericarditis may not exhibit evidence of myocardial ischemia in the presence of coronary disease to the same degree that other persons do. Obliterative or adhesive pericarditis as seen in rheumatic heart disease does not interfere with cardiac function, in contrast to the calcified pericardium sometimes found in constrictive pericarditis.

Several types of surgical procedures have been attempted in the past to increase the blood supply to the myocardium of patients with coronary insufficiency. The aim of these procedures has been to increase the blood flow through existing coronary channels or to increase the anastomatic circulation from extracardiac sources. The operations include:

1. Grafting of extracardiac tissues such as pectoral muscle (Beck),[5] lung (Lezius),[6] or omentum (O'Shaughnessy)[7] to the myocardium.

2. Cardio-pericardiopexy, produced by spraying the epicardium and pericardium with an irritating substance such as bone dust,[8c] asbestos (Beck),[8] or magnesium silicate (Thompson).[9] A variety of other chemical irritants have been used,[10] including starch, glycerine, formalin, phenol, sodium morrhuate, and sodium aleurate.

3. Ligation of the coronary sinus[11] with or without coronary artery denervation (Fauteux).[11f,g]

4. Operations on the sympathetic nervous system,[12] including cervicothoracic sympathectomy, stellate ganglionectomy and posterior root section.

5. Transplantation of the internal mammary artery into the myocardium of the left ventricle (Vineberg).[13]

6. Arteriolization of the coronary sinus by anastomosis of extracardiac blood vessels to the coronary sinus, utilizing a vein graft to the aorta (Beck and associates).[14]

Cardiopexy with magnesium silicate (U.S.P. talc) was introduced by Thompson[9a] in 1939. Excellent functional results in patients disabled by coronary artery disease were reported subsequently by Thompson and Raisbeck[15] and by Gorelik.[16] In this report we wish to confirm the good results obtained with this operation. Our findings are based on the clinical results of the operation in thirty-six patients with coronary artery disease.

Before choosing cardio-pericardiopexy with magnesium silicate as the surgical treatment for coronary artery disease, extensive experimental work was carried out on dogs by one of us (A.N.G.).[17] The various surgical procedures for revascularization of the myocardium were carried out in several series of animals. After repeating these experiments cardiopexy with magnesium silicate was chosen as the best method because of its simplicity, reasonable safety, and because it gave good results in protecting the animal from myocardial infarction and sudden death when the coronary arteries were subsequently ligated.

EXPERIMENTAL OBSERVATIONS

A brief summary of the experimental results will be given. Cardiopexy was produced in 160 dogs and at intervals of ten to fourteen days later the following experiments were performed and the effects compared to those in a control series:

1. Clamping for variable periods of time (one second to fifteen minutes) of one to five small coronary branches. All but ten per cent of operated dogs survived. In the control series, 30 per cent died immediately, probably of ventricular fibrillation, 20 per cent within two weeks and the remainder one to six months later.

2. Clamping of a main branch of a coronary artery. The results were similar as in experiment 1. All but 15 per cent of operated dogs survived, whereas all the control dogs died, 50 per cent immediately and the remainder at intervals up to eight months postligation.

3. Sutures were placed around one to five coronary branches and gradually tightened until complete closure occurred. Fifteen per cent of the dogs subjected to preliminary cardiopexy died whereas all the control dogs died, 35 per cent immediately and the remainder at various intervals up to four months later

4. The main coronary branches were ligated and severed one by one until finally the left coronary artery was severed at its exit from the aorta. Twenty per cent of the operated animals died; all the control dogs died. Great skill and care were required in tying and severing the coronary branches. Sometimes three or four interventions were necessary before the vessels could be dissected clearly, ligated and severed.

5. In the last series of experiments, all the main branches of the coronary arteries were severed at once near their exit from the aorta, one week following cardiopexy. Twenty-five per cent of the dogs died; all the unoperated dogs died.

The results of these experiments convinced us that cardio-pericardiopexy was the simplest and safest surgical procedure which produced a prolonged effect on experimentally produced coronary insufficiency.

AUTOPSY OBSERVATIONS

The introduction of magnesium silicate into the pericardial sac produces a foreign body reaction, inflammatory in type, involving the epicardium, pericardium, mediastinum, pleura, and lungs. A characteristic effect of the reaction is a severe hyperemia of the myocardium, pericardium, and surrounding structures, which begins in a few hours and persists for several weeks to several months. The hyperemia opens up the existing intercoronary anastomotic channels which are not in use. It also stimulates the formation of new intercoronary channels and new extracardiac collateral vessels. As the acute inflammatory reaction subsides adhesions form between the epicardium, pericardium, and mediastinum. These adhesions are vascular and contain blood vessels which penetrate the myocardium and anastamose with the coronary vessels.

Owing to the insufficient lymphatic supply of the pericardium and the large size of the powder particles, very little if any, of the powder is removed from the pericardial sac. A small amount is removed by phagocytosis but the greater amount of the powder remains indefinitely fixed in the pericardial tissues.

Autopsies in animals and human beings reveal a generalized granulomatous adhesive pericarditis. The granulomatous pericardial layer is thickened and vascular, containing new blood vessels which vary in size from microscopic to grossly visible vessels.

Pericardial constriction has never been observed although the pericardium is intimately adherent to the myocardium. Any myocardial infarcts which are present may become revascularized through the collateral vessels.

Thompson and Plachta[18] have recently demonstrated the autopsy findings of two patients who died ten and seven and one-half years, respectively, after the cardiopexy operation. In both cases sections of the heart showed numerous collateral vessels of various sizes coursing between the pericardium and myo-

cardium. The magnesium silicate granules were still present in the pericardial adhesions of both hearts. According to Plachta the caliber of the collateral vessels was at least four times the minimal size (50 microns) necessary for providing collateral circulation, as defined by Schlesinger and associates.[2]

Reviewing the pathologic findings in patients subjected to cardio-pericardiopexy, it is seen that the ischemic myocardium is converted to a hyperemic myocardium by the opening up of intercoronary channels and the formation of anastomotic vessels from the pericardium. Thus, the effect of the operation is to increase the blood supply of the myocardium and to alleviate myocardial ischemia and coronary insufficiency. Angina pectoris is abolished or diminished and the working capacity of the patient is increased.

CLINICAL RESULTS

Case Material.—In the past three years we have subjected thirty-six patients to cardio-pericardiopexy. There were twenty-six men and ten women. The ages of the patients ranged from 38 to 70 years; the majority (twenty-six patients) were 50 years or over. All had proved coronary artery disease as evidenced by typical anginal pain on effort and electrocardiographic or other objective evidence of myocardial damage and coronary insufficiency. Eight of the cases were classified as moderately severe, thirteen as severe and fifteen as very severe. The patients in the latter group were all completely disabled, and were unable to carry on any work or physical activity without anginal pain, fatigue or dyspnea. The thirteen patients classified as severe were unable to carry on normal physical activities without disabling symptoms. Eighteen patients had electrocardiographic or other clinical evidence of previous myocardial infarction. Ten patients had roentgenograms or fluoroscopic evidence of marked cardiac enlargement and five patients had chronic recurrent congestive heart failure and pulmonary edema.

Following operation the patients were observed carefully and subjected to periodic examination. The period of follow-up in the patients who survived the operation ranged from one to two months in one case, three to six months in six cases, six to twelve months in ten cases, one to one and one-half years in eight cases, one and one-half to two years in four cases, and two and one-half to three and one-half years in five cases. In these follow-up examinations the patients had a complete physical examination, fluoroscopy and roentgenogram examination of the heart, twelve lead electrocardiogram and, when indicated, a Master two-step exercise test.

Results.—The results of the operation were gauged by the effect on exercise tolerance, the severity and frequency of anginal pain, and the ability to return to work or to increase the amount of work. On this basis the results were classified as excellent in fourteen patients and good in twelve patients. The results also appear to be good in six other patients operated three to six months ago but the follow-up period is too short for proper evaluation.

There were two operative deaths. One patient died during the operation in acute pulmonary edema. He had had a severe status anginosus for several weeks prior to operation. His electrocardiogram was normal at rest but severe RS-T

depressions developed after exercise and emotional excitement. He may have developed acute coronary insufficiency with myocardial infarction during the operation. A second patient with severe coronary disease and old myocardial infarction died suddenly two days after operation. He had tolerated the operation well and appeared to be making an excellent recovery before his sudden death, which may have been caused by another coronary occlusion. Two other patients died during the follow-up period; one six weeks postoperatively of carcinoma of the stomach with widespread metastases, and the other five months postoperatively of a virus infection which precipitated congestive heart failure. The cardiac status of these two patients had been markedly improved prior to their death.

All the patients who survived the operation were able to resume normal or almost normal physical activities without significant disability. This was true even of the group of patients with very severe coronary disease who were completely disabled for a long period prior to the operation by anginal pain or heart failure. To illustrate the beneficial clinical effects of the operation, several short case histories will be presented.

CASE 1.—A man of 56 with severe coronary sclerosis and angina pectoris, arterial hypertension, and cardiac enlargement. The electrocardiogram showed evidence of coronary insufficiency following exercise. The patient had been completely disabled for three years prior to the operation. Since the cardiopexy he has been followed for sixteen months and has made an excellent recovery. He has returned to full-time heavy physical labor in a factory and has not suffered from anginal pain.

CASE 4.—A man of 39 who had had an old posterior infarction of the left ventricle due to coronary occlusion, followed by severe angina pectoris on mild exertion. The patient was completely disabled for six months because of the angina. Following cardiopexy he resumed work as manager of a cleaning and dyeing establishment and performed heavy physical labor without angina.

CASE 6.—A man of 53 with chronic coronary disease, old coronary occlusion with anterior wall infarction, and moderately severe angina pectoris. The patient has been followed for ten months following cardiopexy. Whereas preoperatively he was able to do only light work because of anginal pain he is now engaged in full-time heavy work as a butcher and has no angina.

CASE 11.—A man of 64 with severe coronary sclerosis, calcification of the mitral and aortic valves, chronic congestive heart failure, and angina pectoris. The electrocardiogram showed evidence of severe myocardial damage. The patient had been completely disabled for several years because of the chronic heart failure and had required digitalization and periodic injections of mercurial diuretics. Several weeks after the operation he was able to resume normal physical activity without any disability. The signs of heart failure completely disappeared despite the discontinuance of digitalis and mercurial diuretics.

CASE 12.—A man of 55 who had several attacks of coronary occlusion with anterior wall infarction was also subject to recurrent attacks of acute pulmonary edema due to left ventricular failure. The heart was markedly enlarged on roentgenogram examination and the electrocardiogram showed the typical signs of multiple myocardial infarcts. The patient had been completely disabled by the severe angina and recurrent heart failure. Several weeks following operation he was able to resume his occupation as a shoemaker and for the past year has carried on normal physical activities without any disability.

CASE 18.—A man of 44 who had severe coronary disease and recurrent acute myocardial infarction. The heart was diffusely enlarged and the electrocardiogram showed signs of old anterior and posterior wall infarction. The patient had been completely disabled for one year because of severe angina pectoris on quite mild exertion. He was unable to walk one-half block without anginal pain. Two months following operation the patient returned to full time work in a restaurant and was carrying on fairly active physical work with only minimal anginal pain. He is now able to walk moderate distances without angina.

CASE 19.—A man of 63 with long-standing hypertension, cardiac enlargement, coronary sclerosis, myocardial infarction, and severe angina pectoris. The electrocardiogram showed evidence of marked left ventricular enlargement and myocardial damage. This patient had been completely disabled for six months because of anginal pain and weakness. Several weeks after the operation he was able to return to heavy physical work as an instrument maker and walked five flights of stairs several times daily to and from his place of work without angina or weakness. He has now been followed for more than two years and has been working steadily without loss of time.

CASE 24.—A man of 51 with coronary sclerosis, angina pectoris, and previous myocardial infarction. Roentgenogram examination showed generalized enlargement of the heart. The electrocardiogram showed evidence of right bundle branch block and previous infarction of the diaphragmatic wall of the left ventricle. This patient, a high school instructor, was moderately disabled by anginal pain and his duties were limited to sedentary activities. He has been followed for eighteen months following cardiopexy. He now performs strenuous physical activity without disability, such as acting as a referee in intramural football games during which he is engaged in prolonged running and physical exercise. He is able to carry on his work without any anginal pain.

CASE 25.—A man of 55 with very severe coronary disease, old myocardial infarction, marked cardiac enlargement, and intractable congestive heart failure, had had several acute attacks of pulmonary edema and was completely disabled because of the chronic heart failure. The electrocardiogram showed evidence of old anterior wall infarction. He has been followed for six months after cardiopexy. The signs of chronic congestive heart failure have almost completely disappeared. He requires only an occasional injection of a mercurial diuretic whereas preoperatively he required at least one or two injections a week. He can carry on fairly normal physical activities without symptoms and has been able to return to his business.

The Electrocardiogram.—The electrocardiograms taken postoperatively generally showed the typical changes of acute and subacute pericarditis, namely, RS-T elevation and T wave inversion in the extremity and precordial leads. These changes often persisted for several weeks or months. Eventually, the record returned to its preoperative appearance. It was of interest that the abnormal electrocardiographic findings present preoperatively usually remained unchanged, despite the marked subjective improvement in most of the patients.

Electrocardiograms following two-step exercise tests were performed pre- or postoperatively in nineteen patients. It was noted that the postoperative exercise tests remained positive in twelve patients despite the marked clinical improvement in their anginal syndrome. In two patients the postoperative exercise tests became negative.

Preoperative Preparation.—Prior to operation the patients were observed for short periods in the hospital. Several electrocardiograms were obtained in most of the patients to exclude the presence of acute coronary insufficiency or myocardial infarction. If signs of congestive failure were noted treatment with digitalis and mercurial diuretics was administered until the signs of failure disappeared. The patients were moderately sedated to allay anxiety and apprehension.

Postoperative Management.—This consisted of sedation and opiates as necessary for pain, an oxygen tent for twenty-four to forty-eight hours, and oral and parenteral antibiotics to prevent pleural or pulmonary infection. All the patients developed some degree of pleuritis, pleural effusion, pulmonary infiltration, or atalectasis. The latter was treated by encouraging the patient to blow into a rubber balloon during the early postoperative period and by early mobilization and ambulation. The pleural effusion was rarely sufficient to warrant chest tap.

In only one patient did significant pleural infection occur. In this case, one of the earliest cases of the series, it became necessary to drain the left pleural cavity surgically because of secondary empyema and recovery was uneventful. In the majority of cases the febrile reaction lasted one to two weeks but after the first forty-eight hours the temperature rarely rose above 101°. Despite the febrile reaction the patients were encouraged to sit up out of bed on the first or second postoperative day and early ambulation was encouraged. The patients were generally completely ambulatory by the end of the first week. The hospital stay averaged ten to fourteen days.

Postoperative roentgenogram examination of the chest generally showed some increase in the size of the cardiac shadow suggesting pericardial effusion. This rarely became marked and cardiac tamponade was never observed. Follow-up fluoroscopic and roentgenogram examinations revealed that the heart size always returned to the preoperative state. No evidence of constrictive pericarditis was ever observed. There was never clinical evidence of impaired venous return or filling of the heart, such as elevated venous pressure, right heart failure, or diminished cardiac pulsations fluoroscopically.

In cases in which congestive heart failure had been present prior to operation, adequate digitalization, salt-free diet, and mercurial diuretics were continued during the postoperative period. In several cases, paroxysmal auricular fibrillation occurred postoperatively. This was always transient and stopped spontaneously or following the oral administration of quinidine. Several of our patients were subject to paroxysmal auricular fibrillation or tachycardia prior to operation. In these patients the arrhythmia disappeared entirely or became infrequent postoperatively.

COMMENT

Our results indicate that cardio-pericardiopexy (Thompson procedure) can be expected to produce a good collateral circulation in patients with coronary sclerosis. Angina pectoris is abolished or markedly diminished and exercise tolerance is strikingly improved in the majority of patients subjected to this operation. The great majority of patients who had been partially or completely disabled were able to return to their normal work or physical activities. Some patients, in fact, resumed strenuous physical exertion ordinarily not permitted to patients with coronary insufficiency and old myocardial infarction. A striking effect of the operation reported by many of the patients was a sense of well-being and the disappearance of fatigue and lethargy. They acquired a zest for living and carrying on their activities which had been lost before the operation.

The immediate and delayed mortality rate was quite low. The immediate operative mortality rate in the thirty-six cases was 5.5 per cent. This is surprisingly low in view of the fact that most of the patients had severe coronary disease and were poor surgical risks. Any type of operation in such patients can be expected to cause fatalities but the mortality rate was kept low by meticulous care of the patient during the operation and postoperative period.

The low mortality rate to be expected from this operation gives cardiopexy an advantage over other effective surgical procedures such as arteriolization of

the coronary sinus. Although recent reports[14] indicate that the latter operation is effective in decreasing coronary insufficiency, it is a longer and more formidable procedure with a higher mortality rate. For this reason, we believe that at the present time cardiopexy is the operation of choice for the surgical treatment of coronary disease when medical treatment has failed to decrease angina pectoris or increase exercise tolerance to the point where the patient can carry on useful physical activities.

SUMMARY

1. Cardio-pericardiopexy with magnesium silicate was performed in thirty-six patients with coronary artery disease who were partially or completely incapacitated by coronary insufficiency or congestive heart failure.

2. During the follow-up period ranging from three to forty-two months, over three-fourths of the patients have exhibited good or excellent clinical improvement as manifested by decreased angina pectoris, increased exercise tolerance, and ability to return to work.

3. The immediate operative mortality rate was 5.5 per cent (two cases). Two other patients have died of noncardiac causes during the follow-up period.

4. It is concluded that this surgical procedure for revascularization of the myocardium should be applied more widely in the treatment of coronary insufficiency.

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VAGAL SENSITIVITY AND THE PRODUCTION OF AURICULAR FIBRILLATION IN EXPERIMENTALLY HYPERTHYROID DOGS

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AURICULAR fibrillation frequently complicates clinical thyrotoxicosis. Nahum and Hoff[1] reported production of transient auricular fibrillation in four thyrotoxic patients by methacholine chloride administration. They postulated that during the action on the auricles of a predisposing factor (E factor), superimposed vagal stimulation may precipitate auricular fibrillation. Experimental observations indicate that anoxemia and auricular distention[2-4] may act as such predisposing factors. Whether a mere excess of thyroid hormone can act as such a factor on an otherwise normal heart is questionable. Furthermore, there is no clear evidence of increase in cardiac vagal tone or vagal sensitivity in hyperthyroidism.

It has been reported that experimentally hyperthyroid dogs do not spontaneously develop auricular fibrillation.[5] We have investigated whether such dogs have increased cardiac sensitivity to acetylcholine and whether auricular fibrillation develops more readily with acetylcholine and methacholine during hyperthyroidism than during euthyroidism.

During hyperthyroidism our animals showed no change in the minimal amounts of acetylcholine producing second degree atrioventricular block, and an increased tendency to fibrillate was seen in but one animal.

METHODS

Ten mongrel dogs fed meat and commercial kennel diet were tested under pentobarbital sodium anesthesia (25 mg./kg. intravenously) five to seven hours after feeding (Series 1, dogs 1 to 5) or eighteen hours or more after feeding (Series 2, dogs 6 to 10). Two additional dogs (11 and 12) received no anesthetic. All were placed on the right side on a table and Lead II was recorded with a direct writing electrocardiograph.

The minimal amount of intravenous acetylcholine (minimal blocking dose) producing second degree atrioventricular block was determined. The determinations included demonstration that at least two smaller doses (decrement of 0.02 mg. if minimal blocking dose was 0.1 mg. or less, and 0.1 mg. if minimal blocking dose was 0.2 mg. or more) failed to produce block. The minimal blocking dose was taken as a measure of cardiac sensitivity to vagal stimulation. Arbitrarily

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chosen doses ten to forty times as great as the minimal blocking dose (10x, 20x, etc.) were given intravenously in attempts to induce auricular fibrillation. In dogs 6 to 10 after acetycholine administration, methacholine chloride was given intravenously in doses from 0.25 to 3.0 mg. for the same purpose, while dogs 11 and 12 received methacholine chloride only. Freshly prepared solutions of acetylcholine and of methacholine in volumes of 0.1 to 1.0 ml. were given as rapidly as possible through a twenty-two or twenty-five gauge needle into the left foreleg vein, with care to avoid more than momentary presence of blood in the syringe before injection. Recording of Lead II was started just before injection and continued until the major alterations in rhythm had vanished or until it was apparent that block would not appear. At least three minutes separated the injections of smaller doses of acetycholine and fifteen minutes those of larger doses and those of methacholine. Return of the electrocardiogram to control type was required before each reinjection.

Determinations were made before, during, and sometimes weeks after daily desiccated thyroid feeding or daily intramuscular thyroxin injections. Desiccated thyroid U.S.P. 0.3 Gm./kg./day for eighteen days and 0.25 Gm./kg./day for twenty-three to thirty days was given in Series 1 and 2, respectively. Dogs 11 and 12 received 0.38 and 0.50 Gm./kg./day, respectively. Thyroxin was given intramuscularly in an average dose of 5.4 mg. daily for ten days. These amounts raise basal metabolic rate and serum precipitable iodine considerably.[5-8]

RESULTS

The results in Series 1 are summarized in Table I. The initial weights of the dogs are given. Symbol B denotes production of transient second or third degree atrioventricular block without fibrillation, while F denotes the production also of auricular fibrillation. The minimal blocking dose remained reasonably constant throughout, except that it fell with thyroxin administration in dog 5. With the doses used dogs 2, 3, and 5 did not develop auricular fibrillation, either during control experiments or during hyperthyroidism. Dog 1 developed fibrillation with 20x during both euthyroidism and hyperthyroidism, but never with 10x. Dog 4 developed fibrillation with 10x and 20x in the one control experiment and also after 22 mg. of thyroxin had been given in five days. After 32 mg. more were given in the next five days, fibrillation was not provoked by single doses of 10x and 20x.

The results in Series 2 are summarized in Table II. The minimal blocking dose in dogs 6, 7, and 9 remained unchanged, and in dog 10 the minimal blocking dose during hyperthyroidism fell between the two different control values. Dog 8 was the only animal showing a significant decrease in minimal blocking dose during thyroid feeding, and this decrease could not be confirmed since the animal died within eighteen hours after the observations and was disposed of before autopsy could be performed. We presume that death resulted from pulmonary complications, since during the experiment the animal had salivated profusely and had displayed noisy respiration.

With acetylcholine doses of 10x and 40x, dogs 6, 7, and 10 did not develop fibrillation during control experiments or during thyroid feeding, while dogs 8 and 9, in which fibrillation was induced during control determinations, either did

TABLE I. LACK OF EFFECT OF EXPERIMENTAL HYPERTHYROIDISM ON CARDIAC SENSITIVITY TO INJECTED ACETYLCHOLINE AND ON PRODUCTION OF AURICULAR FIBRILLATION IN DOGS. SERIES I

DATE	THYROID DOSE*	DOG 1 11.0 kg.			DOG 2 10.0 kg.			DOG 3 11.0 kg.			DOG 4 4.5 kg.			DOG 5 6.8 kg.		
		MBD	10X	20X	MBD	10X	20X	MBD	10X	20X	MBD	10X	20X	MBD	10X	20X
2/28		.5	B	B	.3	B	B	.3	B	B						
3/5		.5	B	F	.4	B	B	.3	B	B						
3/9	THYROID FEEDING BEGUN															
3/19	4.0	.5	B	F	.4	B	B	.4	B	B						
3/26	5.6	.5	B	B	.4	B	B	.4	B	B						
4/6	THYROID FEEDING DISCONTINUED															
4/9	7.2	.3	B	B	.4	B	B	.5	B	B						
5/6											.08	BF	BF	.1	B	B
5/11		.7	BB	F				.3	B	B						
5/11	THYROXIN INJECTIONS BEGUN															
5/15	22	.5	B	F				.4	B	B	.08	BFB	F	.04	B	B
5/20	54	.6	B	B				.3	B	B	.08	B	B	.06	B	B

MBD = minimal amount of intravenous acetylcholine in milligrams producing second degree atrioventricular block.
10x = a dose 10x MBD.
20x = a dose 20x MBD.
F = atrioventricular block plus fibrillation.
B = atrioventricular block without fibrillation.
*Cumulative amounts in Gm./kg. of desiccated thyroid U.S.P. or in total milligrams of pure crystallin thyroxin. (Roche-Organon).

TABLE II. LACK OF EFFECT OF EXPERIMENTAL HYPERTHYROIDISM IN DOGS UPON CARDIAC SENSITIVITY TO INJECTED ACETYLCHOLINE AND UPON PRODUCTION OF AURICULAR FIBRILLATION BY ACETYLCHOLINE AND METHACHOLINE. SERIES II

DOG NO. INITIAL WEIGHT (kg.)	DATE	DAYS ON THYROID*	ACETYLCHOLINE					METHACHOLINE			
			MBD (mg.)	10X TO 20X		30X TO 40X		.25 TO 1.0 mg.		2.0 TO 3.0 mg.	
				B	F	B	F	B	F	B	F
6	7/18	0	.2	1	0	1	0	2	0	1	0
10.7	7/26	0	.2	1	0	1	0			1	0
	8/31	23	.2	1	0	1	0	0	2		
	9/6	29	.2	1	0	2	0			2	0
	9/7	30‡	.2			2	0			4	0
	10/3		.3			1	0			2	0
7	7/31	0	.3	1	0	1	0	1	0	1	0
9.5	8/2	0	.3	1	0					3	0
	8/30	24	.3	2	0	1	0	1	0	2	0
	9/4	29‡	.3	1	0					1	0
	10/3		.3	1	0					1	0
8	8/1	0	.3	1	0	1	0	0	2	0	1
13.2	8/6	0	.2	1	1						
	8/31†	23	.07	3	0	2	1	2	0		
9	8/7	0	.4	1	0					1	0
9.5	8/10	0	.4	6	3					1	0
	9/4	24	.3	2	0	1	0			1	0
	9/6	26	.3§	3	0					3	1
10	8/8	0	.2	2	0					0	2
7.2	8/10	0	.05	1	0	1	0			1	0
	8/11	0						2	3		
	9/5	23	.09	2	0	1	0	3	0		

The figures in columns 5 to 12 indicate the number of times auricular fibrillation resulted (F) or failed to result (B) from intravenous injection of the dose indicated.

*Daily dose 0.25 Gm./kg.

†Died within eighteen hours after experiment.

§Not determined, assumed value.

‡Last day of thyroid feeding.

Other symbols as in Table I.

not develop fibrillation during thyroid feeding (dog 9) or did so only with a larger multiple of the minimal blocking dose (dog 8; the fibrillating dose on both Aug. 6 and Aug. 31 was 2.0 mg.).

Methacholine administration to dog 7 did not precipitate auricular fibrillation before or during thyroid feeding, while in dogs 8 and 10 it induced fibrillation in control determinations but not during thyroid feeding. Fibrillation was not seen in dog 6 during two control experiments but was provoked during thyroid feeding on Aug. 31. However, the arrhythmia did not recur with larger doses of methacholine on two later occasions after additional thyroid administration. In dog 9 after twenty-six daily thyroid doses of 0.25 Gm./kg., 2.0 mg. methacholine twice failed to induce fibrillation, while 3.0 mg. given twice induced fibrillation once. This dog developed a gangrenous lesion of the mouth and had to be discarded without additional testing.

In summary, in ten dogs tested under pentobarbital anesthesia hyperthyroidism produced no increase in sensitivity to acetylcholine except dubiously in dogs 5 and 8. An increased tendency to fibrillate with either acetylcholine or methacholine might be suspected only in dog 9. Fibrillation provoked during hyperthyroidism lasted no longer than during euthyroidism.

TABLE III. INCIDENCE OF AURICULAR FIBRILLATION INDUCED BY INTRAVENOUS METHACHOLINE CHLORIDE IN UNANESTHETIZED DOGS FED THYROID

DOG NO. DATE	DOSE (mg.)	1.0		2.0		3.0		4.0	
	Wt. (kg.)	B	F	B	F	B	F	B	F
11									
2/27	12.7			1	0	4	0		
3/1						3	1		
	THYROID FEEDING 0.38 Gm./kg./day 3/7 TO 3/26								
3/22	9.9	1	0	1	0	1	3		
3/27	9.0	0	1	0	1	0	1		
4/2				0	2				
4/23	10.8			2	0	2	1		
	THYROID FEEDING 0.38 Gm./kg./day 4/26 TO 5/23								
5/24				1	0	3	0		
6/17	11.4					2	0	1	0

	DOSE (mg.)	0.12		0.25		0.50		1.0		2.0	
	Wt. (kg.)	B	F	B	F	B	F	B	F	B	F
12											
3/1	9.6					0	1	0	1	0	2
3/5	9.5	4	0	1	2	0	1				
	THYROID FEEDING 0.50 Gm./kg./day 3/7 TO 3/26										
3/22	9.4	1	0	1	0	1	1	0	2		
3/27	8.6					2	1	0	2		
6/17	8.6			1	0	1	0	1	0	2	1

F = Atrioventricular block plus fibrillation.
B = Atrioventricular block without fibrillation.

Table III summarizes the findings in two periods of thyroid feeding with dog 11 and one period with dog 12. Both dogs were tested with methacholine chloride and without anesthesia. In dog 11 a definitely increased tendency for the auricles to fibrillate was found during and immediately after the first thyroid feeding period, but not immediately after the second period which was of longer duration. In dog 12 in which auricular fibrillation was easily provoked during euthyroidism, the arrhythmia was no easier to induce during thyroid feeding. Three months after thyroid feeding fibrillation was much less easily provoked than initially.

DISCUSSION

Nahum and Hoff[1] reported that 0.75 mg./kg. methacholine given subcutaneously produced auricular fibrillation in four thyrotoxic patients, failed in a fifth with questionable toxicity, and always failed in normal humans, cats, and monkeys. They postulated that excess thyroxin is an auricular excitant which may precipitate auricular fibrillation during increased vagal influence and also that increased sensitivity to a vagus substance exists in hyperthyroidism. The report gives the age (32 years) of only one of the four patients and makes no mention of their cardiac status during hyperthyroidism or thereafter. It is now known that intravascular acetylcholine or methacholine may precipitate auricular fibrillation in pithed bullfrogs[9] and in normal dogs, cats, rabbits, and human beings,[10-15] and that intranasal methacholine may produce auricular fibrillation in hypertensive human beings.[16] Anoxia,[2,3,15] anemia,[4] and mechanical stroking of the auricles[2] are reported to increase this action of these agents, although the influence of anoxia has been denied.[10] Convincing evidence is thus lacking that in the absence of other abnormality excess thyroid hormone predisposes auricular muscle to fibrillation during heightened vagal influence.

The production of auricular fibrillation as a consequence of thyroid administration to human beings with apparently normal hearts appears to be a very rare phenomenon. We are aware of only one reported case.[17] Our data confirm that the hyperthyroid canine heart does not show spontaneous auricular fibrillation.[5] In addition, we find no increased sensitivity to the blocking action of acetylcholine in such hearts. Because of the absence of significant coronary atherosclerosis, auricular muscle in dogs is likely to be more nearly normal than in adult human subjects, but canine auricles are also less prone to fibrillate because of smaller size. Responses of the auricles and of atrioventricular conduction to acetylcholine and methacholine are probably similar to those obtained by stimulation of the vagus nerve. While the effects of acetylcholine upon the properties of auricular muscle are more pertinent, we used the production of second degree atrioventricular block as an indicator of sensitivity. This appears justifiable because (a) the changes in conduction to the ventricles produced by minimal blocking dose injection are invariably accompanied by changes in P-wave contour identical during euthyroidism and hyperthyroidism, thereby indicating that thyrotoxicosis does not alter the relationship between the changes in intra-auricular conduction and those in atrioventricular conduction caused by a given biologically graded dose of acetylcholine; (b) the P-wave changes seen with injection of a low minimal blocking dose during anemia are identical with those produced by the higher minimal blocking dose required in the absence of anemia. Changes in sensitivity of auricular muscle to acetylcholine, therefore, probably closely parallel changes in atrioventricular conduction.

The doses of acetylcholine and methacholine used in attempts to provoke fibrillation are large, causing asystole for periods up to 30 seconds with acetylcholine and 150 seconds with methacholine. Disappearance of the P wave, marked QRS and T changes, marked apnea, profuse salivation, urination, and defecation were frequently seen. The use of larger doses seemed inadvisable. The minimal amount of intravenously injected methacholine producing second

degree atrioventricular block in Starling heart-lung preparations and in euthyroid dogs under pentobarbital anesthesia has been reported as being about 0.12 mg.[2]

The method is open to criticism since the production of fibrillation is inconstant, but a better method for repeated trials in intact animals is lacking. While a larger number of injections would have enhanced the statistical value of our finding we believe that any decided increase in tendency for the auricles to fibrillate during hyperthyroidism would have been revealed in our results. Such increase did not appear in one dog previously tested[10] and in our animals appeared clearly only in dog 11 (Table III), but then failed to reappear during a second period of thyroid feeding. The cause for this failure is not clear. If the increased tendency for the auricles to fibrillate during the first feeding period was causally related to hyperthyroidism, its failure to reappear during the longer second period possibly might have been due to greater depression of thyroid gland function with a consequent lesser degree of hyperthyroidism.[8] This possibility seems remote. Since dog 11 was tested without anesthesia any possible inhibiting effect of pentobarbital on auricular fibrillation required evaluation. We have confirmed that the minimal blocking dose in normal subjects is unchanged by light pentobarbital anesthesia,[4] and have determined (dog 11, April 2, and dog 12, June 17, not shown in tables) that production of fibrillation is not inhibited by pentobarbital (25 mg./kg. intravenously).

In 1,000 patients with thyrotoxicosis including 128 with paroxysmal and 69 with established auricular fibrillation, both varieties appeared with increasing frequency over the age of 45 years.[18] Spontaneous postoperative reversion to sinus rhythm occurred in all with the former type and in one-third with the latter.[18] Between the ages of 30 and 59 years the incidence of fibrillation and flutter in hyperthyroidism is much higher in men. It rises markedly in women, but only little in men with age increasing over 59.[19] These age and sex trends are quite similar to those found on necropsy for the development of coronary sclerosis in men and women.[20-22]

The foregoing, together with our experimental results, suggests that in addition to hyperthyroidism some independently altered state contributes to the clinical development of the arrhythmia. One may speculate that auricles with foci of relative ischemia in the presence of increased cardiac work are more prone to fibrillate than normal auricles, and that morphologic vascular change, not necessarily progressive, should most frequently be the cause of such ischemia, since better correlation of incidence of fibrillation with basal metabolic rate would otherwise be expected. Occlusive coronary artery disease in the presence of auricular distention seems conducive to development of fibrillation,[23] and such distention, present in many cases of hyperthyroidism, itself probably tends to reduce auricular blood flow.[24] A high correlation exists between the incidence of paroxysmal auricular fibrillation and the occurrence of pre-existing prolonged P-R interval, presumably of vagal origin, in myocardial infarction[25] and in chronic coronary arterial disease.[26] Occlusion of auricular arteries is reported to cause arrhythmias and the appearance of ectopic auricular foci, auricular flutter, and fibrillation,[27,28] but production of fibrillation is rare. It is conceivable that in thyrotoxicosis, clinical or subclinical ischemic foci may (perhaps in the presence

of increased vagal influence) provide the proper conditions for initiation of fibrillation, even in the absence of radiologically demonstrable auricular dilatation. The influence of such foci may be the reason why only some thyrotoxic human hearts fibrillate and why our observations on dogs differ from those in clinical hyperthyroidism. It must be admitted, however, that the presence and relationship of ischemic foci to auricular fibrillation in hyperthyroidism remain to be demonstrated.

Since auricular fibrillation occurs spontaneously in a small number of apparently normal hearts, the possibility remains that in some thyrocardiacs it is due solely to an altered state of the muscle without any histologic abnormality. Whether increased tendency to fibrillate would have appeared with prolonged maintenance of our dogs in hyperthyroidism as it seems to in the human disease[18] we cannot state.

While findings in dogs may not properly be translatable to human beings, our results suggest that vagal sensitivity in human hyperthyroidism is not enhanced as has been postulated. Evidence for increase in vagal activity due to hyperthyroidism per se is scanty.[29] It seems probable that fibrillation ensues when for any reason cardiac vagal influence is heightened, and the proper local conditions exist.

SUMMARY

Twelve dogs were made hyperthyroid, ten by feeding of desiccated thyroid, while four, including two of the ten mentioned, were given thyroxin intramuscularly. It was found that, (1) during experimental hyperthyroidism spontaneous auricular fibrillation was not seen, (2) the minimal amount of intravenously injected acetylcholine producing second degree atrioventricular block was not significantly different during euthyroidism and hyperthyroidism, (3) with large intravenous doses of acetylcholine or methacholine an increased tendency for the auricles to fibrillate was detected in only one of fifteen periods of thyroid administration.

The findings are interpreted as indicating that no increased cardiac sensitivity to vagus substance is present in canine experimental hyperthyroidism. Since, (a) the relation of age and sex to the incidence of auricular fibrillation in clinical hyperthyroidism resembles that of age and sex to the incidence of coronary atherosclerosis, (b) a large percentage of patients with hyperthyroidism and auricular fibrillation show evidence of organic heart disease, (c) no correlation exists between the height of the basal metabolic rate and incidence of auricular fibrillation in thyrotoxicosis, and in view of the experimental findings presented, it is suggested that the induction of auricular fibrillation in thyrotoxicosis is influenced by increased vagal activity in the presence of some state independent of the thyrotoxicosis. It is speculated that auricular ischemia may be conducive to the development of fibrillation and that coronary vascular disease, not necessarily progressive, may be present and favorable to initiation of the arrhythmia in a large fraction of the thyrotoxic patients with fibrillation, but no other evidence of organic heart disease.

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Clinical Reports

ATRIAL CONDUCTION DISTURBANCE ATTRIBUTED TO PRONESTYL

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THE USE of procaine amide (Pronestyl) has recently become increasingly popular both with the internist and the surgical anesthetist for prevention and treatment of ventricular arrhythmias. The effect of Pronestyl Hydrochloride on atrial function is commonly thought to be minimal and we have been able to find only one report mentioning the occurrence of atrial dysfunction attributed to clinical Pronestyl Hydrochloride administration.[1] We recently observed a patient in whom atrial conduction disturbance appeared to develop repeatedly coincident with Pronestyl Hydrochloride administration and promptly cleared on discontinuance of the drug.

CASE REPORT

L.A.T., a 69-year-old white veteran of World War I, was admitted to the Jefferson Barracks Veterans Administration Hospital on Jan. 14, 1952. He had been admitted to this hospital on two previous occasions, in April, 1950, and in March, 1951, for bladder diverticulectomy with transplantation of the right ureter and, following this, for repair of a postoperative abdominal hernia. Exhaustive work-up at the time (because of a history of rectal bleeding and melena), revealed only a duodenal diverticulum, psoriasis, and left intermittent eustachian tube occlusion. Albuminuria and pyuria were also found present at that time.

Following his discharge from the hospital the patient continued to feel poorly. Swelling of the legs was first noted six months prior to this admission. He was digitalized by his local physician. The patient interrupted his digitalis medication at one time for approximately two months with marked worsening of his condition. One month prior to the present admission he began to experience progressive dyspnea on exertion, paroxysmal nocturnal dyspnea, and weakness. He was redigitalized two weeks prior to his present admission and took 0.1 Gm. of digitalis leaf until two days preceding his entry into the hospital. His appetite remained good, and there were no ocular symptoms of digitalis intoxication noted. The patient was on a low salt diet.

Physical examination revealed a short, slender, elderly white man, who was afebrile, had a pulse of 80 and a blood pressure of 140/75 mm. Hg. Examination of the head, eyes, ears, nose, and throat was normal, except for arci seniles, fundic arteriosclerotic changes of a moderate degree, and edentulosity. The neck was negative. Examination of the chest revealed an increase in anteroposterior diameter with fair respiratory motion. The lungs were clear to percussion and auscultation. The heart was markedly enlarged in the transverse diameter with enlargement

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particularly of the left ventricular component. The rhythm appeared to be grossly irregular with a few brief regular runs interspersed. The heart tones were distant and no murmurs were heard. The abdomen was slightly protuberant and an infra-umbilical scar was noted. Liver, kidneys, and spleen could not be felt, but some tenderness was noted over the hepatic area. No masses were felt. The remainder of the physical examination appeared entirely within normal limits.

Roentgen examination revealed marked cardiac enlargement in the transverse diameter, both to the right and to the left, although there was noted prominence of the left ventricular segment. There was also slight elongation and tortuosity of the aorta. An upper gastrointestinal series revealed only a large duodenal diverticulum measuring approximately 5 cm. in diameter.

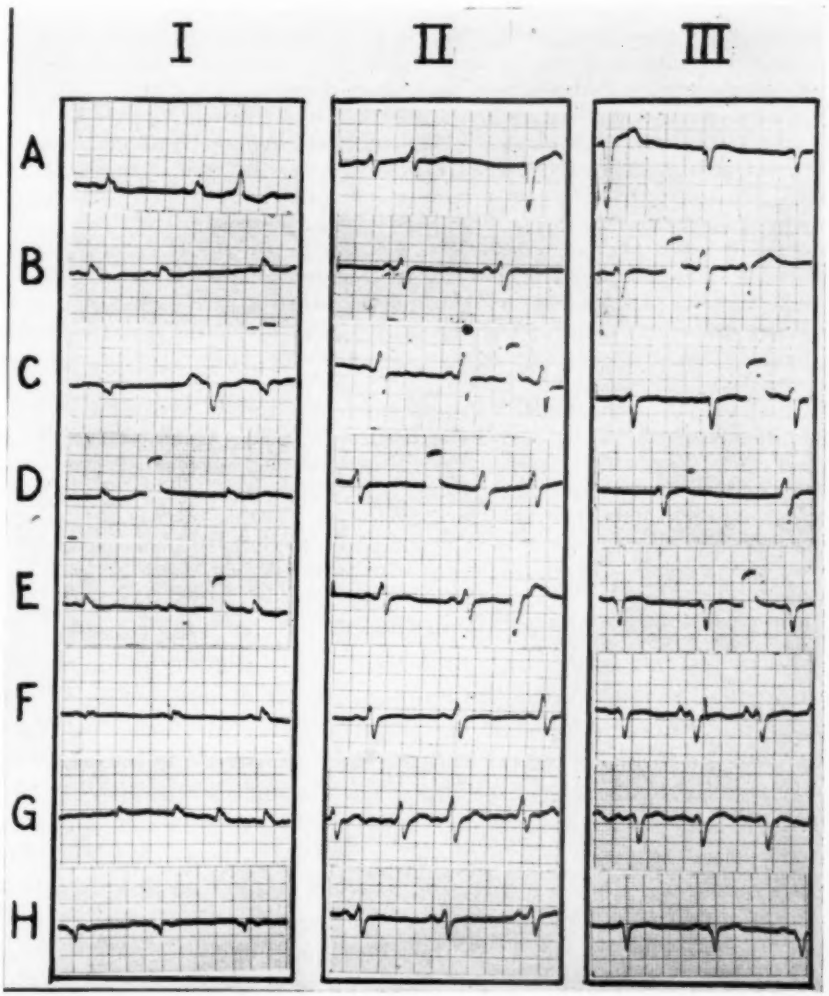

Fig. 1.—Leads I, II and III:

A: 1-16-52. Sinus rhythm with ectopic beats from multiple foci. No Pronestyl.
B: 1-28-52. Sinus rhythm with VPCs. No cardiac drugs.
C: 2- 1-52. Sinus rhythm with VPCs. First day on Pronestyl—500 mg. q8h.
D: 2- 2-52. Nodal rhythm with VPCs. Two days on Pronestyl—500 mg. q8h.
E: 2- 4-52. Sinus rhythm with VPCs reestablished. Off Pronestyl.
F: 2-20-52. Sinus rhythm. On Pronestyl—250 mg. q8h since 2-14-52.
G: 2-21-52. Atrial fibrillation. On Pronestyl—250 mg. q8h since 2-14-52.
H: 2-22-52. Sinus rhythm reestablished. Off Pronestyl.

Urinalyses were done at frequent intervals and albuminuria between trace and 2-plus was consistently present. Specific gravity ranged between 1.005 and 1.012. Microscopic examinations showed varying numbers of white blood cells and cellular casts, the leukocytes varying from as few as 5 cells per high-power field to urines loaded with white cells and casts at various times. Phenolsulfonphthalein retention test revealed moderate impairment of dye excretion. Urea clearance test was 68 per cent of normal. Bromsulfalein test showed no retention. Blood chemistry studies were found to be within normal limits, as were hematological examinations.

Electrocardiograms were done almost daily, and all of them revealed a left bundle branch block pattern (Fig. 1). At the time of the patient's admission until Jan. 31, 1952, many premature contractions from multiple foci were noted, with premature ventricular contractions predominating.

The patient was placed on Pronestyl, 500 mg. every eight hours on Jan. 31, 1952. On Feb. 2, 1952, after the patient had been on Pronestyl for two days, he developed a nodal rhythm. Following this observation Pronestyl was immediately discontinued and sinus rhythm with frequent ectopic beats re-established itself promptly within twenty-four hours. Because it was thought that the Pronestyl administration might have resulted in development of a nodal rhythm, Pronestyl was given intravenously on Feb. 14, 1952. Five doses were administered of 100 mg. each over a period of approximately ten minutes and after injection of the first 100 mg. premature contractions disappeared completely. Five hundred mg. intravenously did not result in disappearance of P waves. Following this the patient was placed on 250 mg. of Pronestyl every eight hours and almost complete suppression of premature contractions persisted. After six days on this medication the patient was found to have developed atrial fibrillation. On Feb. 21, 1952, Pronestyl was again discontinued and on Feb. 22, 1952, the patient was again observed to be in normal sinus rhythm with only very rare ventricular premature contractions present.

Between Feb. 2, 1952, and Feb. 19, 1952, electrocardiograms were taken daily, and normal sinus rhythm with only very rare ventricular premature contractions persisted. Over the entire period of his hospitalization the patient had received no digitalis. Although it was felt strongly that in this patient there was observed an unusual toxic reaction to Pronestyl manifested by depression or disturbance of normal auricular activity, the staff did not feel justified in administering Pronestyl again to absolutely confirm this fact in consideration of the risk possibly being involved in induced depression of atrial activity. At no time during this hospital admission was the patient in manifest cardiac failure. He was discharged from the hospital on March 19, 1952.

DISCUSSION

Only one instance of interference in atrial conduction in the human being by Pronestyl could be found cited in the literature which was reviewed. Fox and associates[1] observed development of complete atrioventricular block and subsequent ventricular fibrillation on Pronestyl administration in one of their cases. It is unknown by what mechanism Pronestyl influences ventricular arrhythmias. It is thought to depress ventricular irritability by some means. Specifically, the refractory period as measured by the Q-T interval is prolonged. Whether the effect of Pronestyl is due to a direct action of a circulating drug or whether its effect is mediated through either the nervous system or some humoral mechanism, or both, has not been clarified. It has been postulated that the efficiency of Pronestyl lies in its diminution of the oxygen requirement of ventricular musculature and the cardiac conduction system, or, conversely, perhaps in a participation in intracellular oxidative processes to increase oxygen utilization by these tissues.[2] The effect of Pronestyl on atrial function appears to be minimal. A high incidence of atrial premature contractions in Joseph's experimental series was thought by him to be due to a relative decrease in total number of arrhythmias.[2] Atrioventricular nodal rhythms were frequently observed to be associated with deep anesthesia regardless of procaine administration.[2,3,4]

Kayden and associates[5] state that toxic effects of Pronestyl have been limited to the gastrointestinal and circulatory systems. Anorexia, nausea, and vomiting were observed on high oral therapeutic schedules (6 to 8 grams a day). Transient electrocardiographic changes were seen in about one-third of the patients receiving a single dose, and such changes may persist in patients on prolonged oral treatment. These changes consisted in widening of QRS and Q-T intervals and decreased amplitude of QRS and T waves. Excess intravenous administration of procaine amide may cause or accentuate hypotension. This complication was not encountered on oral therapy. Too rapid administration of the drug is thought to have resulted, in at least one case, in ventricular fibrillation.[5] At least three cases of agranulocytosis and one of chills and fever attributed to Pronestyl have been recorded.[6,7,8]

Kinsman and associates[9] found that electrocardiograms taken on normal subjects showed slight prolongation of the QRS component and of the Q-T interval as well as transient T-wave changes, which consisted of flattening, notching or inversion of the T waves. The same type of change was noted by them in the patients with disturbances of rhythm. In two of thirty-four patients with arrhythmia, classical left bundle branch block developed following the administration of 250 mg. and 350 mg., respectively, of Pronestyl intravenously. This lasted for 12 minutes in the first and 40 minutes in the second case. There were three other patients in this series who already had bundle branch blocks at the time procaine amide was injected. The QRS duration in these patients was increased by 30 to 40 per cent. This effect persisted from 20 to 50 minutes.

Mark and associates[10] studied the physiologic disposition and cardiac effects of procaine amide. Absorption of the compound from the gastrointestinal tract was rapid and essentially complete. It was found that 50 per cent to 60 per cent of the administered dose of procaine amide was excreted unchanged and 2 per cent to 10 per cent as free and conjugated para-aminobenzoic acid in the urine. They did not feel that the drug accumulated in the body. However, the effect of impaired renal function on drug excretion was not commented on. Also studied were toxic effects on the heart of large doses of procaine amide administered intravenously to a dog. They observed the successive effects of procaine amide on the heart of the dog receiving slow intravenous infusion to a fatal termination. The succession of events was normal sinus rhythm, prolongation of the P-R interval, widening of the QRS complex, wandering pacemaker, nodal and ventricular premature contractions, ventricular tachycardia, and, finally, ventricular fibrillation. However, the total amount of drug administered was 260 mg. per Kg. over a one-half hour period. Wedd and associates[11] concluded that procaine amide may be particularly dangerous when there is disease in the junctional tissues, a finding which was present in our case where left bundle branch block had been consistently noted.

In the present case, probably only a third trial could have conclusively established the etiological role of Pronestyl. Development of nodal rhythm on one occasion and of atrial fibrillation on another occasion was observed only while the patient was on Pronestyl and subsided both times promptly on discontinuance of its administration. Whether a diminished renal function associated with a

chronic pyelonephritis might have led to accumulation of the drug is subject to speculation as is the question of whether this patient's atrial muscle was unusually sensitive to Pronestyl. It is quite possible, however, that identical disturbances may have been observed by others, but not attributed to Pronestyl.

SUMMARY

1. The case of a patient with arteriosclerotic heart disease and pyelonephritis in whom nodal rhythm developed on one and atrial fibrillation on another occasion during Pronestyl administration has been presented. Both times the atrial conduction abnormality promptly subsided on discontinuance of Pronestyl therapy.

2. Pronestyl toxicity in its various manifestations has been briefly reviewed.

3. The potential dangers of procaine amide administration in the presence of disease in the junctional tissues have been emphasized.

ADDENDUM

Since preparation of this report, a series of clinic notes on toxic Pronestyl effects appeared in the Journal of the American Medical Association **149**:1390-1394 (Aug. 9, 1952). No phenomenon similar to the one dealt with in this report was apparently noted.

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